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THIOURACIL AND THYROTOXICOSIS

BY
JOHANNES THYSSEN

EINAR MUNKSGAARD
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THIOURACIL AND THYROTOXICOSIS

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ET TOXICOLOGICA
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Denne Afhandling er af det lægevidenskabelige Fakultet antaget til offentlig at forsvares for den medicinske Doktorgrad.

København, den 30. November 1946.

MOGENS FOG,
h. a. dec.

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PREFACE

The present work was carried out in the period from January 1944 to April 1946. The clinical part was performed during my appointment as assistant in the Pathological Department of the Copenhagen County Hospital in Gentofte, the Chief Pathologist of which, Dr. A. Søeborg Ohlsen, in September 1943 called my attention to certain thyroid problems. In my work with these, I got acquainted with the specific effects of thio-uracil on the thyroid. I wish to acknowledge my indebtedness to Dr. Søeborg Ohlsen for the excellent working conditions afforded me, for his inspiring interest in my work and for his assistance in estimation of the histological material.

The experimental part of the work was performed in Løvens kemiske Fabrik, the proprietor of which, Mr. K. Abildgaard, chemical manufacturer, has placed all the material required at my disposal and thus has rendered me an invaluable assistance for which I give him my heartiest thanks.

Mr. E. Keiding, C. E., Assistant Director of Løvens kemiske Fabrik, called my attention to the thio-uracil problem, and I wish to thank him for his stimulating interest in my work and for encouraging discussions.

I further wish to thank the chief of the Biological Laboratory of Løvens kemiske Fabrik, Mr. M. Tønnesen, Pharm. D., and the chief of the Synthesis Laboratory, Mr. H. Henning Hansen, Pharm. M., as well as Miss Erna Larsen, laboratory assistant, and Mr. Valdemar Hansen, stable master, for their valuable assistance in the daily work.

The clinical part of the work was carried out in the Medical

and Surgical Departments of the Copenhagen County Hospital, Gentofte. To the chiefs of these departments — Professor P. Morville, Dr. E. Rosling, Dr. M. Siggaard Andersen, Dr. O. Kapel, Dr. F. Wulff and Dr. H. Wulff — I wish to give my heartiest thanks for opening their departments to the thio-uracil treatment of patients suffering from thyrotoxicosis, and for their interest in this method of treatment.

My brother, Dr. Erik Pontoppidan Thyssen, has assisted me in the animal experiments. Mr. Th. Ingwar, C. E., has helped me in the plotting of the many curves. Under the difficult conditions during the German occupation, Mr. Christian Rasmussen, Librarian, has been untiring in his efforts to procure for me the literature required. Naturally, I am greatly indebted to them for all their kind assistance.

Finally, I wish to express my gratitude to Løvens kemiske Fabriks Legat for economical support of my work. Furthermore, I am greatly obliged for all the assistance and kindness shown me by many of the personnel of Løvens kemiske Fabrik, as well as of the Medical and Surgical Departments of the Copenhagen County Hospital.

Copenhagen, May 1947.

JOHS. THYSSEN.

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PART I.

EXPERIMENTAL BIOLOGICAL INVESTIGATIONS

INTRODUCTION

In the latter part of 1943, when the German occupation had excluded Denmark from scientific communication with other countries, we read in some photocopies of "The Lancet" that had reached us via Sweden about some interesting observations made in America concerning a specific effect on the thyroid function of certain sulphur-containing chemical compounds (in particular, thio-urea and thio-uracil) — and, with even greater interest, about the preliminary therapeutic results of these substances in thyrotoxicosis.

In animals the administration of these substances for some days produced an enlargement of the thyroid, which histologically showed considerable hyperplasia, accompanied by a state of hypothyroidism in the animals. This effect could not be prevented by iodine if thyroxin was given at the same time, or if the rats had been hypophysectomized beforehand.

In patients suffering from thyrotoxicosis, these substances made the thyrotoxic symptoms commence to subside after a short latent period, accompanied by a fall in metabolism. The effect of the substance was assumed to be due to an inhibition of the synthesis of the thyroid hormone.

At that time the writer was working in the Biological Department of Løvens kemiske Fabrik, Copenhagen, with the question about the interaction between the thyroid, hypophysis and ovaries and it was decided at once to look further into these interesting and promising problems.

As the experiences already gained with these substances in other countries were accessible to us but to a very slight extent, it

seemed more rational to start from the beginning. In carrying out this work, therefore, particular attention has been paid to such experiments as might be of significance to the clinical employment of the substances, whereas experiments that might contribute to elucidate the effect of the substances on the cellular activity of the thyroid were not carried through systematically.

The strumogenic effect of thio-urea and thio-uracil could be confirmed at once — also that thio-uracil is superior to thio-urea in this respect. In addition, however, it was found that — in contrast to the reports received — the toxicity of thio-urea is not only greater than that of thio-uracil but even so marked that it seemed too dangerous for clinical use.

After the first orienting, experimental-biological studies, in February 1944 — in the Copenhagen County Hospital, Gentofte — treatment of patients suffering from thyrotoxicosis with thio-uracil was commenced at the same time as the experiments were continued.

In the meantime, in Løvens kemiske Fabrik, we had soon tried out a number of substances near related to thio-urea and thio-uracil, with a special view to their strumogenic effect in rats — in order, if possible, thus to find some substance possessing an even greater effect and thus perhaps more suitable for therapeutic purposes. We arrived at the result that methylthio-uracil has a considerably greater strumogenic effect than has thio-uracil, while the toxicity of the two substances is about the same. In April 1944, therefore, methylthio-uracil was introduced in the clinic, gradually replacing thio-uracil. Also phenylthio-uracil was found to have a strong strumogenic effect, but in one patient suffering from thyrotoxicosis the result obtained with this compound was so discouraging that we desisted from further therapeutic employment of it.

The effect of thio-uracil and methylthio-uracil on the animal organism under varying experimental conditions has been studied rather thoroughly — and likewise the effect of these substances on the state of hyperthyroidism in patients. Particular attention has been paid to the problem of dosage and possible untoward effects in the patients treated with these remedies.

During the further course of the present work, in particular after the capitulation in May 1945, at which time the practical part of the work was nearly concluded, a comprehensive literature on the whole subject finally reached this country. This literature has been reviewed as thoroughly as possible. In order to make the whole matter more easily surveyable and to avoid unnecessary repetitions, instead of giving a collective review of the literature, I have chosen to deal with the appertaining literature within the individual sections of my work and compare my own results with those reported by other authors.

First, a brief orienting survey of the goiter problem is given. In order to attain a thorough recognition of this symptom complex, numerous experimental biological investigations have been carried out — in particular, in the last two decades — especially after it had been established that certain food elements have strumogenic effect in animals. Particular mention is made of the investigation which, among other things, resulted in the discovery of the strumogenic effect of thio-urea.

Chapter 1

GOITER AND STRUMOGENIC SUBSTANCES

According to *Marine*[123], the function of the thyroid consists in the circumstance that through its iodine-containing secretion it makes it possible to maintain a higher metabolism than could be attained otherwise. *Harington*[70] likewise emphasizes the stimulating effect of the thyroid hormone on the metabolic processes, but he states that details concerning this effect are obscure.

Through its hormone the thyroid gland is of decisive importance to the rate of practically all physiological processes of the organism; and variations in the amount of this hormone in the organism may clinically manifest themselves very strikingly.

Generally the term "goiter" means any pathological enlargement of the thyroid, no matter whether it be accompanied by an increased, normal, or decreased output of thyroid hormone. It has long been known that endemic goiter occurs in districts where iodine is lacking in the drinking water, and that goiter is encountered only in regions where the normal iodine supply is lowered — and also that iodine is a specific remedy against goiter (*Rosenquist*[165]). *Hercus & Purves*[73] consider a low iodine supply to be prerequisite for the frequent occurrence of goiter, and they emphasize strongly that in New Zealand as well as anywhere on the earth where these conditions have been investigated, iodine deficiency has been found to be the predominant factor in the development of goiter. In this connection it is to be mentioned that *Hayden, Wenner & Rucker*[72] have been able to produce goiter in rats kept on an iodine-deficient diet.

Marine[123] found that the first effect of iodine deficiency on the thyroid is hypertrophy and hyperplasia of the gland, with loss of

colloid, decrease in its iodine content, increased vascularization of the parenchyma, growth of the epithelial cells of the follicles and new-formation of follicles. The last finding, however, has been questioned by *Means*[135]. On physiological compensation, these changes subside.

Iodine is essential to normal thyroid activity, and the iodine content of the thyroid decreases with the increasing hyperplasia (*Marine & Lenhart*[128]). The same authors emphasize that a certain minimal iodine content of the gland is required to preserve its normal structure. *Means*[135] has pointed out that the iodine content is an accurate measurement for the normal reserve of the thyroid; and he states that hyperplasia appears when the iodine content of dried thyroid substance falls below 0.1 %. *Marine*[123] thinks that the thyroid enlargement itself is merely the anatomical expression for the specific physiological disturbance, whereas the anatomical changes constitute a constant, highly sensitive and objective indicator for the course, degree and intensity of the disturbance. He takes the changes arising in the thyroid in simple or endemic goiter, in thyrotoxicosis, in compensatory hypertrophy or on administration of thyrotropic hormone to be essentially identical.

Iodine deficiency of the organism may be absolute or relative. When, as emphasized by *Marine*[123], goiter in man occurs most frequently in certain periods of life (fetal life, puberty, pregnancy and lactation), this is possibly attributable to a relative iodine deficiency in the organism in these periods because then particularly great demands are made on the organism and, thus, on the thyroid. Furthermore, *Byars, Friedman et al.*[27] state that seasonal variations in the size and histological features of the normal thyroid probably are due to climatic differences, corresponding to the varying thyroid hormone requirements of the organism in the various seasons.

The fact that not all persons living in a goiter region acquire goiter, and that not all goiter patients have the same degree of goiter, has to be taken to indicate that various factors play a rôle in the development of goiter. Among such factors, *Rosenquist*[165] mentions a number of endogenous and exogenous ones. Thus, among the endogenous factors the following are recorded: age, sex,

race and hereditary disposition, the latter of which are reckoned by *Marine*[123] to play no particular rôle. In contrast hereto, *Dunhill*[40] takes the hereditary factor to be rather significant in this connection. Among the exogenous factors, Rosenquist mentions drinking water, in which, besides the iodine content, also the calcium content appears to play a rôle. Experimentally, *Williams*[202] was able to produce iodine deficiency in animals by administration of calcium salts, as these interfere with the iodine metabolism.

Another important exogenous factor is the diet. The significance of the diet as a strumogenic factor in experimental animals has been elucidated through a great number of investigations, several of which are to be mentioned here, as, for one thing, the recognition of the strumogenic effect of thio-urea was a result of these studies.

McCarrison[114] (1920) showed that a diet very rich in protein and fat may produce thyroid hyperplasia in pigeons. *Mellanby & Mellanby*[136] were able to demonstrate similar changes in dogs given a diet rich in fat, especially butter; in particular, under this treatment the thyroid would sometimes increase to five times its normal size. Further, *Marine*[123] states that swine liver may produce goiter in dogs and fish.

In 1928 *Chesney, Clawson & Webster*[31] observed that a diet of cabbage together with oats and hay produced goiter in rabbits. Histological examination of the large thyroid in these animals showed a diffuse, parenchymatous hyperplasia. Simultaneous with these changes in the thyroid, *Webster et al.*[197] found the heat production and the rate of metabolism in these animals to be lowered. In addition, they were able to show that administration of iodine brought about a rise in the metabolism, and that there was a certain parallelism between the amount of thyroid hormone produced and the amount of iodine present — besides, that the hyperplastic thyroid glands were able to produce the hormone but were lacking in iodine.

Marine, Baumann & Cipra[124] *and Spence, Walker & Scowen*[182] were able to confirm that cabbage has a strumogenic effect. Through biopsy the last-mentioned authors made sure that the

thyroid did not beforehand show a histological picture of hyperfunction. *Hercus & Perves*[73] found a greater strumogenic effect from hay and oats than from cabbage; and *Marine*[123] states that the strumogenic effect may vary in different samples of lucerne-hay, and that the variation does not depend entirely on the iodine content.

Treatment with light (*Webster*[194]) and with heat (*Marine, Baumann & Cipra*[124]) increases the strumogenic effect of cabbage — possibly because light and heat destroy certain enzymes that are able to destroy the strumogenic factor in the cabbage. Drought may lower the effect (*Spence, Walker & Scowen*[180], *Spence*[179], *Webster*[194]), and wet weather increases the effect (*McCarrison & Madhava*[116], *Spence*[179]). In keeping with this, *Marine, Baumann, Webster & Cipra*[127] found that compressed cabbage (*i. e.*, cabbage from which the press-juice is removed) has a greater strumogenic effect when it is washed with water — something that hardly may be explained as due to removal of iodine by the washing, but rather suggests that struma-preventive substances are removed by the washing, while the strumogenic factor itself is insoluble in water. The same authors have been able to show that certain fresh plants may prevent the strumogenic effect of the cabbage, and they state that this inhibitory effect apparently is associated with ascorbic acid. *Spence*[179] mentions that cabbage contains a substance which promotes the tissue oxidation and thus may facilitate the thyroid function; he arrived at the conclusion that this substance must be ascorbic acid. As early as 1931, *Marine*[122] emphasized that cabbage appears to contain both the strumogenic factor and an antistrumogenic factor, stating that ascorbic acid seems to be the unstable antistrumogenic factor. Thus, vitamin C appears to be able to inhibit the effect of the strumogenic factor in cabbage. According to *Spence*[179], however, vitamin C deficiency is of no significance to the development of goiter in animals kept on a cabbage diet; and the same applies to deficiency in vitamins A, B and D.

Even though the occurrence of antistrumogenic factors is an interesting fact, it is the strumogenic factor itself that is of the greatest importance in this connection.

According to *Marine, Baumann et al.*[124, 126], the way in which

the strumogenic factor exerts its effect is still obscure. These authors think, however, that the effect on the thyroid is due to a relative lack of iodine, which again results from an increased demand for thyroid hormone in the organism. This increased demand may be induced most readily by preventing the tissues from utilizing the ozygen, and these authors hold indeed that the effect on the thyroid takes place through an inhibition of oxidative processes in the tissues — an inhibition which the thyroid tries to compensate.

Webster[194], trying to enter further into the question about the strumogenic factor, was able to show that this is connected with a positive factor, and that its effect is not brought about by deficiency in some substance or other.

Marine, Baumann, Spence & Cipra[126] emphasize that all plants belonging to the Brassica genus exert a strumogenic effect, and they all contain mustard oils. These oils are not in themselves strumogenic, but they can be converted into cyanides which have a considerably inhibitory effect on the tissue oxidation. Indeed, these authors found the cyanides able to produce hyperplasia of the thyroid, although — according to *Bruman & Mildwarf*[25] and *Spence*[179] — this does not take place regularly. Iodine inhibits this effect, just like iodine inhibits the strumogenic effect of cabbage, meat diet, and anterior pituitary extracts or partial thyroidectomy[126].

Further, it is to be mentioned that, according to *Spence*[179], cyanides increase the excretion of thiocyanate, which he found not to have any antithyroid effect. On the other hand, *Rawson, Hertz & Means*[156] found that patients treated for hypertension with thiocyanate were liable to develop a goiter; and *Williams*[202] ephasizes that the substance interferes with the formation of the thyroid hormone and decreases the amount of this hormone in the organism.

This strumogenic effect is not specific for rabbits but may be induced, among others, in rats too (*Webster & Chesney*[196], *Hercus & Purves*[73]). The effect is produced not only by cabbage, hay and oats, but it has been demonstrated also in all examined plants belonging to the Brassica genus, to which cabbage belongs. Further-

more, besides by lucerne, the effect may be produced also by other leguminous plants, *e. g.*, pea-nut *(McCarrison*[115]) and soy bean *(McCarrison*[115], *Sharpless*[175]).

Marine, Baumann, Spence & Cipra[126] state that administration of iodine prevents all Brassicae from inducing hyperplasia of the thyroid. In contrast hereto, however, *Kennedy & Purves*[95] emphasize that administration of iodine does not prevent the strumogenic effect of Brassica seeds, even though the increase in the weight of the thyroid is reduced noticeably under this treatment. *Kennedy & Purves* give a very thorough account of the effect of rape seed on the thyroid of the rat, and they mention that they also were able to demonstrate hypertrophy of the adrenals — which has also been demonstrated by *Spence*[179] after treatment with methyl cyanide. Further, *Griesbach*[63] found that, at the same time, also histological changes appeared in the anterior pituitary lobe. Besides, *Griesbach, Kennedy & Purves*[64] showed that the thyroid changes failed to appear in hypophysectomized rats, on which account they took an increase in the production of thyrotropic hormone to be far more probable than an increased sensitiveness of the thyroid to this hormone.

During his attempts to isolate the strumogenic substance in rape seed, *Kennedy*[94] arrived at the assumption that the substance very likely might be a derivative of thio-urea, on which account he examined the action of allyl thio-urea in this respect and found that, like thio-urea, it produced the same changes in the thyroid of the rat as rape seed.

Almost at the same time *Richter & Clisby*[162] observed that phenyl-thio-urea in rats produced hyperplasia and hypertrophy of the thyroid; and finally, *Mackenzie, Mackenzie & McCollum*[120] — likewise rather accidentally — found that sulfaguanidine has a similar effect.

These three observations, which all were made very nearly at the same time and independently of each other, show that certain sulphur compounds in rats are able to produce goiter.

Here, then, we meet with well-defined sulphur-containing chemical compounds that have the same effect on the thyroid as has cabbage. Considering, furthermore, that most likely the

strumogenic factor in rape seed is a derivative of thio-urea we have made a step forwards to the solution of the perplexing problems implied by the strumogenic effect of certain plant substances.

The above-mentioned observations, that certain sulphur-containing chemical compounds possess an antithyroid effect, have given rise to a great number of experimental-biological investigations and theoretical views, which so far have resulted in the fact that by means of such substances we now are able to control the increased activity of the thyroid in thyrotoxicosis. Clinical investigations aimed at this particular point were first carried out by *Astwood*[15].

Chapter II

TECHNIQUE AND ANIMAL MATERIAL

The technique employed in the present experiments will be mentioned in part under the various sections of the work.

Experimental Animals.

The animals here employed were albino rats, all belonging to the same strain. This strain originates from the University Institute of General Pathology, Copenhagen; from 1929 to 1932 it was inbred by Dr. *E. Møller-Christensen*, and from 1932 by the Biological Department of Løvens kemiske Fabrik, Copenhagen.

One series of experiments was performed on female and male rats, 12 days old. Otherwise the experiments have been carried out exclusively on female rats, 6 months old, weighing about 200 g, or — in a few experiments — on male rats of the same weight, about 5 months old. It is to be mentioned that, according to *Remington et al.*[161] the male rats continue to gain in weight at a higher rate than the female after the animals have reached a weight of about 150—180 g.

The purpose of employing almost exclusively 6-months-old female rats of about 200 g has been to obtain a basis for comparison of the various substances and dosages employed. Furthermore, as peroral administration of the various substances through an esophageal tube has been employed mostly, it was preferable to use large animals because they are better able to stand this method of dosage. Besides from some preliminary experiments it seemed as if the female rats stand the employment of the tube better than the males.

During the experiments, which all were carried out at a fairly

constant room temperature, the rats stayed in steel-wire cages with steel-wire floor (3 cm above the bottom pan), 5—6 rats in each cage. The cleaning of the cages and feeding dishes has been very careful.

Besides water, the rats were given the following diet:

Rolled oats	18 parts
Rolled barley	18 —
Wheat germs	20 —
Lucerne flour	4 —
Pea flour	10 —
Caseinogen	8 —
Palm-nut oil	12 —
Icelandic whale-oil	10 —

The young rats were given milk instead of water, and the same applies to the rats submitted to an operation. In numerous control experiments this diet has not shown any strumogenic effect in rats.

Chemical Compounds.

All the chemical compounds employed in the experiments were prepared in the Synthetic Laboratory of Lovens kemiske Fabrik by Mr. H. Henning Hansen, Pharm. M. After their preparation, they were control-tested in the Control Laboratory by Mr. P. Mørch, Pharm. M., chief of this laboratory. In every instance the results of these tests confirmed the identity of the substance analyzed.

No particular mention is to be made here of the various chemical substances, nor of the procedure for their control analysis.

Whether or not the substances are soluble in water, after being weighed off exactly, they are ground in mortar together with gum arabic mucilage till the consistence of the mixture is uniform. Then they are suspended or dissolved in water or 0.9 % sodium chloride solution with addition of altogether 5 % gum arabic mucilage, which in control experiments showed no undesirable effect in the animals.

A fresh suspension or solution has been made up for each experiment or — in protracted experiments — at intervals of 3—4 weeks.

The durability of thio-uracil in aqueous solution within this period has been examined by Mr. P. Mørch, who has not been able to demonstrate any noticeable destruction of the substance within this period

Fig. 1. Introduction of the esophageal tube on a rat.

Methods of Administration.

The chemical compounds employed were given to the animals in the following ways: perorally, subcutaneously or intraperitoneally.

Oral Dosage.

In order to know precisely how much of the substance employed has been ingested by the animals, instead of giving it dissolved in water or mixed with the food, it has been given through an esophageal tube. Each dose is always given in 1 ml water containing 5 % mucilage.

For introduction of the esophageal tube, the animal is first made to gape over a wedge-shaped stick of wood provided with a hole,

through which the tube is to be introduced. This procedure is shown in Fig. 1.

The tube here employed has been a Mercier catheter No. IX (the most suitable size for this purpose), which in this way cannot be bitten into pieces by the animal. After rapid, but cautious introduction of the catheter for 6—7 cm, the suspension is injected by means of a 1 cc Record syringe, mounted on the catheter. The suspension is always shaken very thoroughly before its application. The entire procedure of its ingestion takes but 2—3 seconds.

After numerous tubing experiments with varying procedures, the writer found the above method, described by *Pedersen-Bjergaard*[153a] to be the most serviceable.

Subcutaneous Dosage.

For this way of administration the single dose is suspended or dissolved in 0.5 ml, saline with addition of 5 % mucilage and injected under the skin of the back.

Intraperitoneal Dosage.

This has been employed only in experiments concerning the toxicity of the substance. As here the single dosage often has been very large it was always suspended or dissolved in 3 ml saline containing 5 % mucilage. The injection was given in the lower part of the abdomen; and during the injection the animal was held with its head down.

Weighing of the Animals.

All the rats were weighed on the same scales, with an accuracy of 1 gram, and always immediately before the commencement of the experiment, sometimes at regular intervals during the experiment, and 24 hours after the administration of the last dose.

Autopsy.

24 hours after the administration of the last dose, the animals were killed with illuminating gas in a glass flask equipped for this purpose, and then the organs were removed immediately after.

Thyroid. — After opening of the body, this gland is removed in toto together with the trachea and larynx, whereafter it is

separated from these organs. This separation is very easy after removal of the fascia covering the thyroid. Then the gland is placed on a glass plate and carefully freed from connective tissue — bluntly with a pair of pincers, sharply with a small pair of scissors. Rats presenting only one thyroid lobe are discarded. In the removal of the thyroid the same procedure is followed closely in every instance.

Pituitary. — After opening of the skull, the brain is removed and then the fold of the dura over the pituitary — by means of fine pincers — whereafter the pituitary is loosened and removed in toto without any particular difficulty.

Ovaries, uterus, liver, spleen and kidneys require no particular mention. The uterus is weighed only after being freed from fluid.

Weighing of the Organs. — After the removal, the organs are freed from the adipose and connective tissues attached, and as a rule weighed immediately after; if this is not done, the organs are placed in a closed Petri dish on filter paper moistened with saline. Immediately before their weighing, all the organs are rolled on dry filter paper in order to remove the moisture on the surface.

The organs are always weighed on the same scales — an analytical balance with an accuracy at 1/10 mg.

Preparation of Organs for Histological Examination.

Immediately after weighing of the organs that are to be examined histologically, they are fixed in 10 % formalin solution and later treated in the usual manner with dehydration in alcohol and embedding in paraffin; then sections are cut on microtome at a thickness of 5 μ. All the sections are stained with hematoxylin-eosin.

Operations on Rats.

Operations have been performed exclusively on female rats, 6 months old, weighing about 200 g.

Thyroidectomy, Hemithyroidectomy.

The rats are placed in a closed glass flask with a piece of cotton moistened with ether. As soon as the animal is anesthetized — which takes but a short time — it is placed on a wooden plate and fastened, lying on its back. The anesthesia is maintained by

placing a pledget of cotton, moistened with ether, over the nose of the animal.

The anterior aspect of the neck is washed with alcohol. Then a longitudinal incision is made in the midline, the subcutis and the fasciae are divided, and the pretracheal musculature is pulled aside by self-retaining retractors.

Hemithyroidectomy: If there is any noticeable difference in the size of the two lobes, the larger has always been removed — bluntly, with pincers. Ligation to the arteries of this lobe has been performed only if they were particularly large. Hemorrhage has been checked carefully by tamponade together with a hemostatic. Then suturing of the skin with continuous silk.

Thyroidectomy: After many operations with varying procedures, the following was found to be the most serviceable: After uncovering of the thyroid with removal of the overlying fascia, only the largest of the arteries to the thyroid is ligated. Then both lobes together with the isthmus are removed bluntly — as a rule without any particular difficulty. The hemorrhage is checked as described above. Then the wound is closed by suturing with silk.

The thyroid tissue removed is prepared for histological examination as described above.

Several of the thyroidectomized rats died immediately after the operation. Some had stridorous respiration immediately after the operation and died within 48 hours; 1 rat died from postoperative hemorrhage; and 1 rat had a subcutaneous emphysema, which subsided.

After the operation the rats were placed in incubators and given milk instead of water. Only the rats in which the operation and the postoperative course were uncomplicated were employed for subsequent experiments.

Gaddum[58] states that thyroidectomy is not difficult, whereas injury to the nervus recurrens, which lies closely to the thyroid, may easily take place. No doubt, such injury has been the reason for the above-mentioned stridorous breathing. *Gaddum* further states that the rat has only two parathyroid glands, which unavoidably are removed at the same time, on which account the operated animals generally have symptoms of tetany, but these subside regularly when the animals are given milk.

Controls.

Several of the control animals are mentioned in detail under the various sections. Control weights for female rats of 6 months and male rats of 5 months are given in Table 1.

TABLE 1

Control Animals.

	Body-weight	Thyroid weight	Pituitary weight	Ovarian weight	Uterine weight
I	10 female rats, 6 months old.				
Average	205 g	13.4 mg	8.8 mg	78.0 mg	441 mg
μ *)	14	1.9	1.9	16.6	147
II	10 male rats, about 5 months old.				
Average	210 g	10.3 mg	5.5 mg		
μ	12	1.7	0.8		

*) Se p. 29.

Here it is to be mentioned that in the experimental rats (females of 6 months, about 200 g) in which the treatment produced no change in the histological picture of the thyroid (see Chapter III) the values recorded for the thyroid weight corresponded very closely to those found in the controls.

For comparison it may be mentioned that the normal thyroid weight in female rats of 200 g, according to *Christensen*[33], is 13—19 mg. Remington et al.[161] gives 12—21 mg for both female and male rats of about 200 g, finding no particular sex difference in this respect. The latter authors review the results reported by many other investigators, showing that the average thyroid weight in rats of about 200 g varies from about 15 to 22 mg. *Jensen & Kjerulf-Jensen*[87] state that in rats the normal thyroid weight is: $10 + 0.1 \times$ (weight of rat in grams minus 60) $\pm$ 20 %, which gives even higher values.

Probably this very wide variation of the values for the thyroid weight in normal rats of 200 g has to be explained in part by the circumstance that the rats on which these values were calculated were not all of the same strain, partly by variations in the amount of strumogenic and antistrumogenic factors as well as iodine in the food of the animals — besides to the care with which the thyroid is dissected out.

The histological examination of the thyroid in the controls shows a fairly uniform picture from one animal to another, both in females and males. The follicles are large, filled with strongly colored colloid, in which marginal vacuoles are seen here and there. The follicular epithelial cells are rather low; the interfollicular connective tissue is scanty with normal vascularization. The

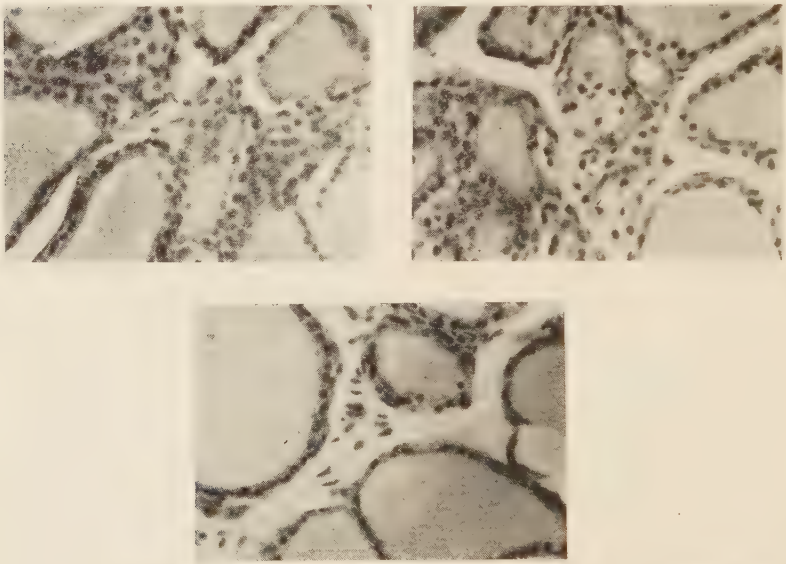


Fig. 2. Microphotos of the thyroid from untreated female rats, 6 months old. (Magnif. × 400).

pictures show only slight evidence of histological activity (Fig. 2). Variations in the slight histological activity of the thyroid may be seen in the various animals as well as in various sections from the same gland.

It is to be mentioned that experiments were carried out in all seasons, and that no attention was paid to this in estimating the results.

Accuracy of the Experimental Results.

In order to estimate the dispersion of the experimental results, a calculation of the mean error has been carried out after *Hartmann*[71].

For this calculation the following procedure was employed: The experimental result for each experimental animal within a concluded experiment is designated respectively O_1, O_2 ..... O_n. The average value of these findings is: $O_m = \frac{O_1 + O_2 + \ldots + O_n}{n}$

In the text the uncertainty of the experimental results within each concluded experiment is designated as μ *(mean deviation)* and is defined as:

$$\mu = \sqrt{\frac{(O_1 - O_m)^2 + (O_2 - O_m)^2 + \ldots\ldots + (O_n - O_m)^2}{n - 1}}$$

According to *Hartmann*[71], it is probable that in a long series of experiments 68 % of the results of the individual experiments will fall within $O_m \pm \mu$, while 95.5 % will fall within $O_m \pm 2\,\mu$, and 99.7 % within $O_m \pm 3\,\mu$.

Apart from a few exceptions, the standard deviation on the body weight of the rats is calculated only for the control animals.

Furthermore, a great number of random tests have shown that the weight of the animals after the experiments varies in the same manner, on which account no calculation of the mean error has been carried out for this feature too.

Strumogenic Effect with Reference to the Species, Sex and Age of the Animals.

Species.

For experimental biological investigations with employment of strumogenic substances, most authors have employed rats. It is generally agreed that rats are highly serviceable for this purpose: the changes in the thyroid appear rapidly, attaining quite considerable degrees with regard to the size of the gland as well as to the histological evidence of hyperactivity.

Mice react in the same manner as rats (*Mackenzie & Mackenzie*[121], *Freiesleben, Kjerulf-Jensen & Meulengracht*[52]).

Enlargement and hyperplasia of the thyroid are produced by the strumogenic substances also in dogs (*Mackenzie & Mackenzie*[121]) and in rabbits (*Freiesleben* et al.[52]).

Apparently guinea-pigs do not react to this treatment. Thus, the writer found no effect in these animals from 14 days' treat-

ment with thio-uracil. No particular importance is to be attached to these findings, however, as probably the experimental period was all too short. Nor did *Mackenzie & Mackenzie*[121] find any effect on guinea-pigs from treatment with sulfapyridine and sulfaguanidine; but no information is given about the length of the experimental period. The animals received these substances in the food in concentrations from 3/4 % to 1 1/2 %. Larger doses gave anorexia, loss of weight, and then the animals died. Nor were *Freiesleben et al.*[53] able to demonstrate any increase in the thyroid or cellular hyperplasia in this organ in guinea-pigs that were treated with a daily dose of 40 mg of methylthio-uracil for 10—30 days — a dosage which in my experiments on rats has given marked changes in the thyroid. Larger doses are reported to have had a toxic effect.

The histological picture of the thyroid from normal guinea-pigs shows preponderantly large follicles filled with colloid, surrounded by flat epithelial cells. As a rule, only slight evidence is seen of physiological activity. In contrast hereto, sections of the thyroid from a normal rat show a little more pronounced signs of physiological activity.

When guinea-pigs fail to react to the treatment, it is probably because the follicles, filled with colloid, contain a considerable reserve of thyroid hormones. No doubt, the thyroid is susceptible to the effect of the treatment, but this cannot manifest itself until the aforementioned reserve is used — and this requires a considerable experimental period, much longer than the one employed in the experiments mentioned.

Nor did *Mackenzie & Mackenzie*[121] find any effect from the strumogenic substances on chicks of varying age and size. The concentration in the blood of the substance administered was found to be high; and the authors emphasize that the same diet gave effect in rats.

In contrast to these results, *Mixner, Reineke & Turner*[138] were able in chicks to demonstrate the effect of this treatment, even within a relatively short period; and they state that 1-day-old chicks are quite apt for such experiments.

No extensive experiments with many different animal species

have been reported. Very likely, all species have a thyroid that will react to these substances with enlargement and hyperplasia of the parenchyma if the experiments are continued for a sufficient length of time.

TABLE 2.

Thyroid Weight in Male and Female Rats, 6 Months Old, Treated with Thio-uracil and Methylthio-uracil.

Number of rats	Sex	Initial weight	Dose	Weight at end of experiment	Thyroid weight	μ
			Thio-uracil			
11	F.	218 g	10 mg daily by mouth for 15 days	220 g	27.4 mg	3.7
5	M.	217 g	—	230 g	33.3 mg	2.0
			Methylthio-uracil			
11	F.	214 g	5 mg daily by mouth for 15 days	215 g	36.8 mg	9.0
5	M.	224 g	—	243 g	34.8 mg	8.4
12	F.	202 g	2 mg daily subcutaneously for 15 days	215 g	36.4 mg	3.1
11	M.	210 g	—	223 g	35.4 mg	5.5

Sex.

A schematic survey of the strumogenic effect of thio-uracil and methylthio-uracil on female and male rats is given in Table 2, from which it will be noticed that there is no dicisive difference in the effect of the two substances on female and male rats.

Nor have *Freiesleben et al.*[53] found any difference in this respect between the two sexes, whereas *Mackenzie & Mackenzie*[121] state that the enlargement of the thyroid in the female rats exceeds this effect in the males. Similar findings in chicks have been reported by *Mixner, Reineke & Turner*[138].

Age.

Only few investigations have thrown any light on the significance of the age of the animals to the strumogenic effect. In experiments with acetonitrile, *Marie, Baumann, Spence & Cipra*[126] found the thyroid hyperplasia to be more pronounced in young rabbits than in old ones. *Mackenzie & Mackenzie*[119, 121] emphasize

that the increase in the weight of the thyroid under treatment with strumogenic substances decreases with advancing age, and that the same applies to the histological changes in the thyroid though to a lesser degree. They found the enlargement of the thyroid to be inversely proportional to the age of the animal, being more pronounced in the young. They think that as the rat grows older its pituitary becomes less sensitive to deficiency in thyroid hormone, and hence it produces a less pronounced hyperplasia of the thyroid and decrease in the colloid, or the thyroid becomes less sensitive to the thyrotropic hormone.

So, while the sex appears to be of no significance to the strumogenic effect of the various substances, the age of the animal appears to be of rather decisive importance in this respect.

Chapter III

STRUMOGENIC EFFECT OF VARIOUS CHEMICAL COMPOUNDS

The purpose of the studies reported in this chapter was partly to look for chemical compounds with a stronger strumogenic effect than thio-uracil, so that possibly they might prove more suitable clinically in dealing with thyrotoxicosis, partly to compare the chemical constitution of the substances examined and their effect, or lack of effect, on the weight and histological features of the thyroid.

As thio-urea is less effective and far more toxic in its effect than thio-uracil, no particular interest was taken in derivatives of the substance, and — also in order to limit the work reasonably — the main stress was laid on examination of thio-uracil-like substances.

The effect of thio-uracil on the weight and histological picture of the thyroid is dealt with in Chapter V. The experiments show that a daily single dose of 10 mg thio-uracil given by mouth for 15 days gives a very pronounced effect on the thyroid in female rats of 6 months. Besides, this dosage is tolerated by the animals without any inconvenience. Therefore, it was decided to adopt a dosage of 10 mg perorally for 15 days, given to female rats of 6 months, as the standard test dose in studies on the strumogenic effect of other chemical compounds, as this procedure would also make it possible to compare the effect of the substance in question with that of thio-uracil.

For the examination of the various chemical compounds, therefore, the following method was adopted.

Procedure: After the various substances are prepared and controlled through analyses, a portion is weighed off, ground in a

mortar and suspended (or dissolved) in water, containing 5 % mucilage, in such a concentration that 1 ml water contains 10 mg of the substance in question. Then 10 mg (1 ml) is given through an esophageal tube once daily for 15 days to a group of rats. Each substance is tried out in this way. All the test animals have been female rats, 6 months old, weighing about 200 g. Each group has comprised 5 or 6 animals. On autopsy the thyroid has been removed and treated as described already in Chapter II.

Also the estimation of the histological picture was carried out after the method described in Chapter II. Within each group there was a fairly close agreement between the histological pictures presented by the various thyroids. The total result for each group is recorded by means of the symbols 0 or + as follows:

0: no particular changes.
+: distinct evidence of activity in all specimens.
++: pronounced evidence of activity in all specimens.
+++: marked evidence of activity in all specimens.
++++: very marked evidence of activity in all specimens.

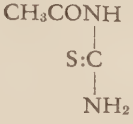
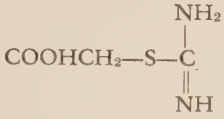
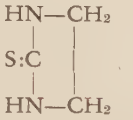
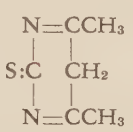
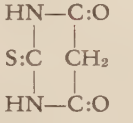
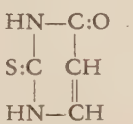
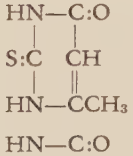
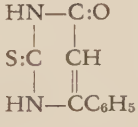
Apart from the substance under examination, the experimental condition has been the same for all the animals. In the case of some substances several different doses were given, each to a group of animals. The results are recorded schematically in Table 3, in which thio-urea and thio-uracil are included for comparison. (The substances marked with asterisk are not mentioned in the literature accessible to the writer.)

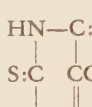
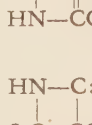
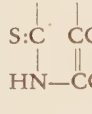
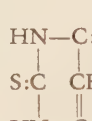
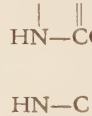
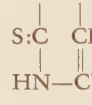
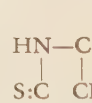
TABLE 3.

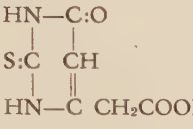
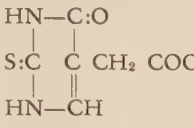
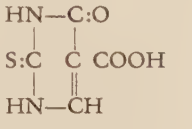
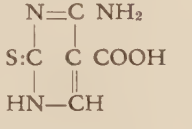
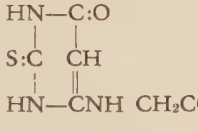
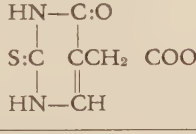
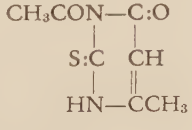
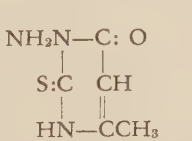
Effects of Various Chemical Compounds Tested on Rats with Regard to Their Strumogenic Action.

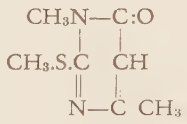
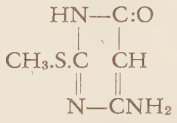
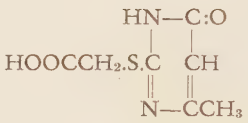
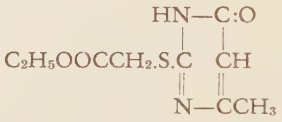
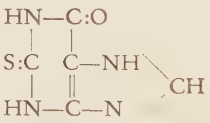
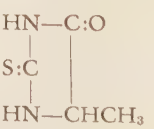
For explanation of the signs employed to designate this effect, see p. 34.

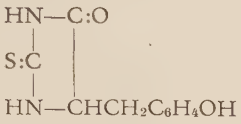
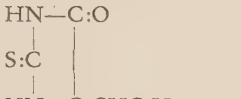
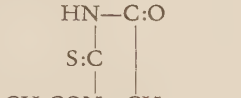
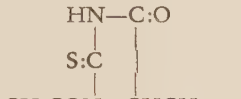
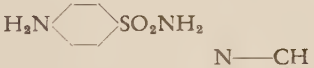
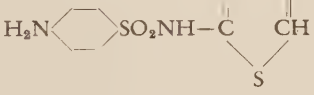
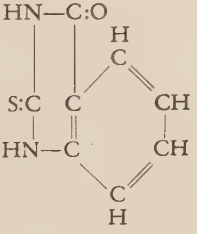
Substance	Constitutional formula	Dose mg	Thyroid weight mg	μ	Histological activity
I.					
Thio-urea and its derivatives					
Thio-urea:	$\begin{matrix} & NH_2 \\ & \vert \\ S{:}C & \\ & \vert \\ & NH_2 \end{matrix}$	10	19.3	5.0	++

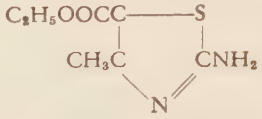
Substance	Constitutional formula	Dose mg	Thyroid weight mg	μ	Histological activity
Acetylthio-urea:		10	16.0	3.0	+(weak)
*Pseudothiohydantoic acid:		10	13.3	1.3	0
N,N'-ethylene thio-urea:		5	35.4	5.4	++
		10	35.3	7.5	+++
*Acetyl acetone thio-urea:		10	14.5	1.3	+(weak)
II. *Pyrimidines, non-substituted.*					
2-thio-4, 6-dioxy pyrimidine: (thiobarbituric acid)		10	14.8	4.3	0
2-thio-6-oxy-pyrimidine *(thio-uracil)*		1	21.8	4.4	+
		5	24.9	4.1	++
		10	27.4	3.6	+++
Pyrimidines, C-substituted.					
2-thio-4-methyl-6-oxypyrimidine *(methylthio-uracil)*		1	27.8	3.3	++
		5	36.8	8.5	+++
		10	39.6	6.7	++++
2-thio-4-phenyl-6-oxypyrimidine (phenylthio-uracil)		1	15.0	1.4	+
		5	31.5	6.1	+++
		10	42.1	9.2	++++

Substance	Constitutional formula	Dose mg	Thyroid weight mg	μ	Histological activity
*2-thio-4, 5-dimethyl-6-oxypyrimidine (dimethylthio-uracil)		1	16.5	2.2	+
		5	20.1	1.7	+
		10	29.9	3.1	++
2-thio-4-methyl-5-ethyl-6-oxypyrimidine (methyl-ethylthio-uracil)		1	15.6	2.9	+(weak)
		5	22.9	3.1	+
		10	28.0	8.7	++
*2-thio-4-methyl-5-benzyl-6-oxy-pyrimidine (methylbenzyl-thio-uracil)		5	19.7	3.9	+
		10	25.6	6.5	++
*2-thio-4-methyl-6-dimethyl-pyrimidine (methyl-dimethyl-thio-uracil)		10	17.1	1.7	+
*2-thio-4-acetyl-amino-6-oxypyri-midine (acetyl-aminothio-uracil)		10	14.0	1.8	0
*2-thio-4-benzoyl-amino-6-oxypyrimidine (benzoylaminothio-uracil)		5	14.8	2.7	0
		10	13.1	3.4	0
2-thio-4-amino-6-oxypyrimidine (aminothio-uracil)		10	11.6	1.3	0
2-thio-4, 5-diamino-6-oxypyrimidine (diaminothio-uracil)		10	11.8	3.4	0

Substance	Constitutional formula	Dose mg	Thyroid weight mg	μ	Histological activity
*2-thio-4-acetic-acid-6-oxypyrimidine (thio-uracil-acetic-acid-4)		5	26.4	3.4	++
		10	32.0	2.7	+++
*2-thio-5-acetic-acid-6-oxypyrimidine (thio-uracil-acetic-acid-5)		10	14.8	1.7	0
*2-thio-5-carboxyl-6-oxypyrimidine (thio-uracil-carbonic-acid-5)		10	19.7	4.4	+
*2-thio-5-carboxyl-6-amino-pyrimidine		10	13.3	1.3	0
*2-thio-4-amino-acetic-acid-6-oxypyrimidine (amino-acetic-acid-thio-uracil)		10	15.0	3.1	0
*2-thio-5-acetic-acid-ethylester-6-oxypyrimidine)		10	11.8	2.5	0
Pyrimidines, N- and C-substituted.					
*1-acetyl-2-thio-4-methyl-6-oxypyrimidine (N-acetyl-methylthio-uracil)		10	19.8	3.7	+
*1-amino-2-thio-4-methyl-6-oxypyrimidine (N-amino-methylthio-uracil)		10	16.5	2.6	0
		(10 days, toxic)			(very weak)

Substance	Constitutional formula	Dose mg	Thyroid weight mg	μ	Histological activity
Pyrimidines, mercapto-compounds.					
*2-methyl-mercapto-1, 4-dimethyl-6-oxypyrimidine		10	14.6	2.2	0
*2-methyl-mercapto-4-amino-6-oxypyrimidine		10	16.1	2.7	+ (very weak)
Pyrimidines, thioglycolic acid compounds.					
*2-thio-glycolic-acid-4-methyl-6-oxypyrimidine		10	12.8	1.7	0
*2-thio-glycolic-acid-ethyl-ester-4-methyl-6-oxy-pyrimidine		10	13.4	2.1	0
Purines.					
2-thio-6-oxypurine (thiohypoxanthine)		10	13.8	2.9	0
Thiohydantoins, non-substituted.					
2-thiohydantoin		5	28.6	4.9	++
		10	32.9	3.2	+++
Thiohydantoins, C-substituted.					
*2-thio-4-methyl-hydantoin		5	19.2	2.2	+ (very weak)
		10	17.3	1.9	+ (very weak)

Substance	Constitutional formula	Dose mg	Thyroid weight mg	μ	Histological activity
*2-thio-4-(p-hydroxybenzyl)-hydantoin		10	13.6	2.2	0
*2-thio-4-benzal-hydantoin		5	38.7	7.2	+++
		10	37.1	11	+++
Thiohydantoins, N-substituted.					
*2-thio-3-acetyl-hydantoin		5	25.1	2.6	++
		10	32.4	8.5	+++
*2-thio-3-acetyl-4-methylhydantoin		5	20.6	2.6	+
		10	27.2	2.9	++
Sulfonamides.					
Sulfanilamide		10	15.5	1.7	+(weak)
Sulfathiazole		10	16.7	2.9	+
Other compounds.					
*2-thio-6-oxy-tetrahydrochinazolin		2½	18.6	3.8	++
		5	25.5	5.5	+++
		10	28.9	7.0	+++

Substance	Constitutional formula	Dose mg	Thyroid weight mg	μ	Histological activity
*Amidomethylthio-zol-carbonic-acid-ethyl-ester		10	17.0	3.7	0

Of the 40 chemical compounds mentioned altogether 25 were able to a greater or lesser extent to increase the thyroid weight in rats and produce evidence of increased activity in the histological picture of the glands. In 13 of the 25 active substances the effect was equal to, or greater than, that of thio-urea. With the doses here employed, 8 of the substances were found to have a stronger effect than thio-uracil.

Of all the substances here examined, phenylthio-uracil and methylthio-uracil gave the strongest effect. Taking into account not only the doses of 10 mg, but also the smaller doses (1 and 5 mg; see also Tables 9 and 10), methylthio-uracil has to be looked upon as the most effective substance.

Here it will be appropriate to mention that shortly after this observation and after further examination of the toxicity of methylthio-uracil to rats, we commenced to use this substance clinically for the treatment of thyrotoxicosis, and before long it replaced the use of thio-uracil. Also phenylthio-uracil was tried out, but with unsatisfactory result.

From the experiments here performed it would hardly be justifiable to draw any decisive conclusion as to the effectivity of the other, powerful substances against thyrotoxicosis. To try out these substances thoroughly, however, has been out of the question. Apparently several of the substances employed in doses of 10 mg have had a toxic effect on the rats, as the body weight has been falling during the experiments. This applies to 3 of the 4 derivatives of thio-urea employed, giving an average loss of weight amounting to 9—30 g. All active thiohydantoins were found to give an average loss of weight of 4—8 g. On treatment with methyl-dimenthylthio-uracil the weight decreased on an average by

15 g. In all the groups the loss of weight was fairly alike for all the animals within the group concerned. In doses of 10 mg, none of the other substances produced a loss of weight in the experimental animals. Still, it is to be mentioned that the experiments with N-aminomethylthio-uracil had to be discontinued after 10 days, because the animals looked extremely exhausted without having lost any weight.

Even though, according to these experiments, N, N'-ethylene-thio-urea has a quite considerable strumogenic effect and is even far more easy to prepare than thio-uracil, these observations led to the clinical employment of thio-urea or thio-urea compounds being given up. Something similar applies to the thiohydantoins, among which especially 2-thio-4-benzal-hydantoin proved to be active.

Astwood has examined the strumogenic effect of altogether 106 different substances (J. Pharmacol. & Exper. Therapeutics, *78:* 79, 1943). Unfortunately, it has not been possible for me to obtain this work, but it is reviewed in The Lancet (1943, II: p. 483) in which it says that derivatives of thio-urea and certain aniline derivatives were found to be active. Among the derivatives of thio-urea, 2-thio-uracil proved to be most active and, after this, thiobarbituric acid. The latter substance was found to be quite inactive in the experiments here reported. From a subsequent report (*Astwood, Bissell & Hughes*[17]) it is evident indeed that this substance was not thiobarbituric acid (the original substance was still available), but 5,5-diethyl-2-thiobarbituric acid.

Further, sym-diethylthio-urea and 5-benzal-2-thiohydantoin were found to be active, although in a lesser degree. Among the aniline derivatives, the sulfonamides proved to be active. Finally, it may be mentioned that also o-m-p-aminobenzoic acid was found to be active.

After the conclusion of the experiments mentioned in this chapter, a few additional investigations of similar character have been reported. Thus, *Mackenzie & Mackenzie*[121] mention 21 substances, of which 9 prove to be active, namely: thio-urea, derivatives of thio-urea, derivatives of sulfanilamide, and p-aminobenzoic acid.

In a total of 96 highly different substances, *Jensen & Kjerulf-Jensen*[87] found 21 in possession of a stronger or weaker strumogenic effect; and of these active substances, 15 — including the 9 most active — are derivatives of thio-urea or pyrimidine. The remaining 6 substances are: sulfaguanidine, sulfonal, dithio-oxamide, thio-antipyrine, rhodamine and p-aminobenzoic acid. On going through the results reported by the last-mentioned authors, it is evident that methylthio-uracil is the most active of all the substances examined, and then comes phenylthio-uracil.

Among other authors, mention is to be made of *Christensen*[33], who has examined 8 substances which all are dealt with in the aforementioned works. But *Christensen*[33] employed determinations of the metabolism as the most important criterion of the effect of these substances on the thyroid, stating that only in this way may we obtain some direct information about the function of the thyroid. Determination of the weight and histological examination may be employed for supplementary evidence.

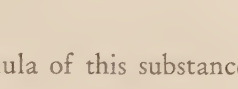
In the other investigations mentioned as well as in the studies carried out by the writer, determination of the weight and histological examination of the thyroid constitute the only basis for an estimation of the strumogenic effect of the various substances.

In Chapters V and VI a comparison is made between the effect of thio-uracil on the weight of the thyroid and its histological features and on the metabolism. The effect on these three different characters shows such a close agreement that it seems fully justified to use the weight determination + the histological examination as criterion of the effect on the thyroid.

Here a review of all the substances examined by the authors mentioned would take us all too far, especially as it is by no means the same substances that are dealt with in the various works. Thus, 24 of the substances examined by the writer are not mentioned elsewhere; in Table 3 these substances are marked by means of an asterisk.

On correlation of the results obtained for the substances mentioned in two or more investigations, they are found as a rule to agree very well. Among the few divergences it may be mentioned that — in contrast to *Astwood* — *Jensen & Kjerulf-Jensen*[87]

found derivatives of sulfanilamide to be inactive. In concordance with *Astwood*, the writer found both sulfanilamide and sulfathiazole to be active, although in a slight degree. In contrast to the writer, *Mackenzie & Mackenzie*[121] found acetyl-thio-urea to be inactive.

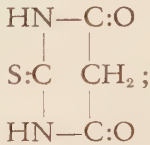
Finally, it is to be mentioned that *Jensen & Kjerulf-Jensen*[87] found ethylene thiocarbamide to be inactive, they give the constitutional formula of this substance as  . A substance with this constitutional formula is designated by the writer as N,N'ethylene thio-urea, and I have found it to be very active.

Chemical Constitution and Strumogenic Effect.

Christensen[33] states that no relation can be found between the action of these substances on the metabolism and their chemical constitution. On the other hand, *Jensen & Kjerulf-Jensen*[87] found the antithyroid effect to be rather specific. Thus, they claim that a C:S radical is present in all distinctly active substances — with sulfaguanidine as the only exception to this rule. To this, among others, sulfanilamide may be added, even though it is only slightly active. The C:S radical is also present in all the substances here examined that showed a distinct strumogenic effect; yet it cannot be considered an absolutely prerequisite of strumogenic activity, even though it appears to be an important factor. On the other hand, the presence of sulfur appears to be more decisive. All strongly or slightly active substances mentioned in the investigations cited here contain sulfur, the only exception to this rule being the aminobenzoic acids, which were found to be active by *Astwood* as well as by *Jensen & Kjerulf-Jensen*[87] and *Mackenzie & Mackenzie*[121]. Still, the last-mentioned authors state that this substance has no effect on the histological picture of the thyroid. *Jensen & Kjerulf-Jensen*[87] found the substance active only when given in very large doses. This is the only one of the 17 examined sulfur-free substances that has any effect.

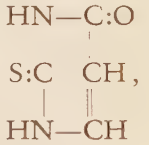
A direct comparison between the chemical constitution of various substances and their strumogenic effect reveals several characteristic conditions.

Thiobarbituric acid has the formula:



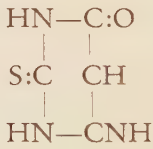
; and this substance is quite inactive.

If the oxygen atom in the 4-position, however, is replaced by a hydrogen atom at the same time as a double binding is introduced, while one of the hydrogen atoms in the 5-position falls out, we have:



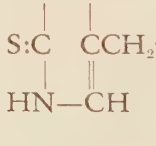
namely: thio-uracil, which is very active.

If now the hydrogen atom in the 4-position is replaced by an NH_2 group, we have:



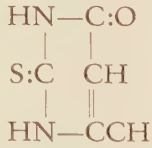
namely: aminothio-uracil, which is quite inactive.

Thio-uracil acetic acid-5



has no strumogenic effect.

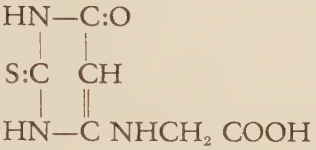
If the acetic acid group is moved down in the 4-position, we have:



, namely: thio-uracil acetic acid-4, which has a strumogenic effect stronger than that of thio-uracil. If substitution has been made beforehand

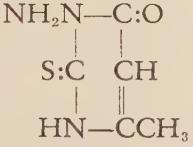
with an amino group in the 4-position, and this then is substituted with an acetic acid group we have:

amino-acetic acid thio-uracil



which is inactive.

Substitution with an amino group appears to abolish or reduce the strumogenic effect. For further illustration of this we may take amino-methylthio-uracil:



, which is only slightly active — in contrast to the highly active methylthio-uracil.

These conditions show that even apparently small variations in the chemical constitution are of decisive significance to the strumogenic effect of the substance, but no definite principle in this matter — no definite relation between chemical constitution and strumogenic effect — can be made out.

The following three facts, however, are to be emphasized:

1. C:S radical has been present in all the highly active strumogenic substances.
2. Sulfur is present in all the examined, highly or slightly active, strumogenic substances with the exception of aminobenzoic acid.
3. Substitution with an amino group reduces or abolishes the strumogenic effect.

Chapter IV

EXPERIMENTS ON THE TOXICITY OF THIO-URACIL, METHYLTHIO-URACIL, PHENYLTHIO-URACIL (MINIMAL LETHAL DOSE). — THIO-UREA

In the literature accessible to the writer, practically only thio-urea and thio-uracil have been employed for therapeutic purposes. As is evident from the studies reported in Chapter III, both methylthio-uracil and phenylthio-uracil have a stronger strumogenic effect than has thio-uracil, which again has a considerably stronger effect than thio-urea. A comparison between the strumogenic effect of thio-uracil, methylthio-uracil and phenylthio-uracil is presented graphically in Fig. 3.

Of all the substances examined so far, methylthio-uracil was found to have the strongest strumogenic effect.

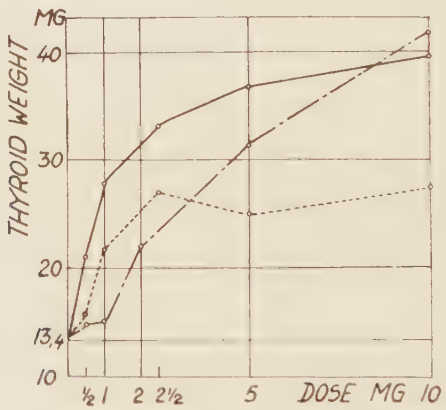


Fig. 3. Curves for the thyroid weight in female rats, 6 months old, treated for 15 days with thio-uracil (o - - - - o), see Table 9; methylthio-uracil (o———o), see Table 10; and phenylthio-uracil (o— - —o), see Table 3.

In view of these findings, it seemed natural to try to employ phenylthio-uracil and, especially, methylthio-uracil clinically in cases of thyrotoxicosis. Before going on to such therapeutic experiments, however, it seemed desirable to compare the toxicity of the two last-mentioned substances with that of thio-uracil and thio-urea.

Procedure.

In order quickly to obtain a fairly reliable estimate of these qualities, it was decided to estimate the "minimal lethal dose" of the substances mentioned. All the experiments aimed at this question were carried out on female rats, 6 months old. Regardless of the size of the dose, all the substances were suspended in 3 ml physiological salt solution (containing 5 % mucilage).

All the animals were given the dose intraperitoneally. Instead of giving the total dose at once, it was distributed on two injections given on two successive days — because these substances are soluble but very slightly, and they are absorbed from the peritoneal cavity but slowly. Autopsy was performed on all the animals that died, and attention was paid in particular to macroscopic changes in the liver and lungs, besides possible mechanical injuries to the abdominal viscera. The findings are recorded in Tables 4, 5 and 6.

TABLE 4.

Female Rats, 6 Months Old, Treated with Intraperitoneal Injection of Thio-uracil (Determination of the Minimal Lethal Dose).

Number of rats	Average weight	Dose	Died	Autopsy
5	200 g	20 mg	0	In all the dead animals, unabsorbed thio-uracil was found in the peritoneal cavity. No injuries. Congestion of the lungs and liver.
5	201 g	60 mg	0	
5	207 g	200 mg	0	
5	188 g	600 mg	5	
5	230 g	400 mg	3	
5	209 g	300 mg	0	
5	213 g	350 mg	2	

TABLE 5.

Female Rats, 6 Months Old, Treated with Intraperitoneal Injection of Methylthio-uracil (Determination of the Minimal Lethal Dose).

Number of rats	Average weight	Dose	Died	Autopsy
5	196 g	20 mg	0	
5	204 g	60 mg	0	As in Table 4.
5	202 g	200 mg	0	
5	188 g	600 mg	5	
5	217 g	400 mg	5	
5	219 g	300 mg	1	
5	212 g	350 mg	5	
5	206 g	320 mg	3	

TABLE 6.

Female Rats, 6 Months Old, Treated with Intraperitoneal Injection of Phenylthio-uracil (Determination of the Minimal Lethal Dose).

Number of rats	Average weight	Dose	Died	Autopsy
5	212 g	350 mg	1	As in Table 4.
5	207 g	400 mg	0	

From Tables 4, 5 and 6 it is evident that the minimal lethal dose for these substances is as follows:

Thio-uracil: 350—400 mg.
Methylthio-uracil: 300—320 mg.
Phenylthio-uracil: $>$ 400 mg.

The difference in the toxicity of methylthio-uracil and thio-uracil should not go against the clinical employment of methyl-thio-uracil in cases of thyrotoxicosis, especially when we take into consideration the greater strumogenic effect of methylthio-uracil.

The toxicity of phenylthio-uracil is low, and — as is evident from Table 3 — it has a quite considerable strumogenic effect on rats when given in a dose of 10 mg. When given in small doses (2 mg and less), however, this effect is considerably less than that of thio-uracil.

On estimation of the strumogenic effect of phenylthio-uracil (Table 3), a quite peculiar and rather puzzling phenomenon was observed: the animals in the groups which received 1/2, 1 and 2 mg phenylthio-uracil daily for 15 days were losing weight. The average loss of weight in response of these doses was respectively: 28, 20, and 21 g. But on treatment with 5 mg of the substance the average weight kept unchanged; and with a dose of 10 mg the average weight increased 8 g.

Thio-urea.

Even in the first orienting experiments with thio-urea, in which this substance was given through an esophageal tube, it was observed that some of the animals died in from a few minutes to 6 hours after a single dose of 10 mg. Furthermore, many of the animals became dyspneic. One rat had convulsions immediately after the injection and died about 5 minutes after. A very careful autopsy was performed on all these animals. In the animals that died within a relatively short time after the injection most of the ingested solution was found in the stomach. No mechanical injuries were found that possibly might explain the death of the animal. All the animals showed pronounced hydrothorax together with hyperemia and edema of the lungs, besides hyperemia of the liver tissue.

Fränkel (1912)[56] states that allylthio-urea in experimental animals causes anesthesia and death from edema of the lungs and hydrothorax; and further, that thio-urea lowers the rates of the pulse and respiration. Besides, the thio-urea compounds have a reflexaccentuating effect, as the central nervous system first is stimulated, then paralyzed.

Lange (1892)[107] found something similar. In rabbits the administration of thio-urea compounds produced serous hydrothorax. The lungs were found to be voluminous, hyperemic and edematous. Besides, there was congestion of the abdominal viscera, especially the liver and kidney, but otherwise no particular abnormality. In dogs, vomiting was a constant symptom on oral as well as intravenous administration. Lange states that this vomiting appears to be of central nature; no irritation of the stomach was seen. In

addition, the dogs showed salivation and their general condition was poor; their movements were wobbly, and sometimes cramp-like muscular contractions were seen. The pulse and respiration were slow and the animals were dyspneic.

Lange[107] was not able to explain the pulmonary edema. It was not due to cardiac insufficiency, but — like the congestion of the liver and kidney — is was rather an expression for the reaction of these organs to the excretion of the substances.

I have tried to estimate the toxicity of thio-urea (minimal lethal dose) to female rats, 6 months old, in the same way as for thio-uracil and methylthio-uracil in the preceding section. As thio-urea dissolves readily in water, the substance was given in aqueous solution but otherwise in exactly the same manner as the two substances mentioned. Even though the experimental conditions were exactly alike in all the tests (same kind of rats; all the doses of thio-urea, the same synthetic preparation), the results vary considerably. These results are recorded in Table 7, in which they are entered after the size of the dose, not in the succession in which they were performed.

TABLE 7.

Female Rats, 6 Months Old, Treated with Intraperitoneal Injection of Thio-urea, given in Two Equal Doses on Two Successive Days.

Number of rats	Average weight	Dose	Died	Autopsy
5	212 g	1 mg	0	
5	205 g	2 mg	1	All the dead animals showed
5	210 g	4 mg	0	hydrothorax, congestion
5	204 g	8 mg	0	and edema of the lungs,
5	209 g	12 mg	1	and congestion of the liver.
15	214 g	14 mg	4	No injuries.
15	220 g	16 mg	5	(NB! All the dead animals
10	213 g	20 mg	2	died after the first injec-
10	215 g	40 mg	2	tion.)
5	219 g	80 mg	0	
5	210 g	160 mg	2	

From these experiments it is not possible to determine the minimal lethal dose. But the studies on this question have not been carried through because some unknown factors appeared to interfere.

Several findings indicate that some of the animals have been hypersensitive to thio-urea, as otherwise it can hardly be explained why some rats died soon after 10 mg thio-urea given by mouth or small doses given intraperitoneally, while other animals (of the same sex, age and size) were able to stand a dose of up to 160 mg given intraperitoneally. In this connection it is also to be emphasized that the animals which died during these toxicity determinations, all died after the first injection, which means that they had received only one half of the dose recorded in Table 7.

The strumogenic effect of thio-urea on rats is considerably less pronounced than that of thio-uracil. In female rats of 6 months the thyroid weight after daily peroral treatment with 10 mg thio-urea for 15 days increased to about 19 mg; after treatment with thio-uracil and methylthio-uracil under the same conditions the values for the thyroid weight were respectively 27 and 39 g.

From the experiments reported in Chapter III it is evident that in rats the strumogenic effect of N,N'ethylene-thio-urea is much stronger than that of thio-urea, and also distinctly stronger than that of thio-uracil. With a view to the possible clinical employment of this substance, some experiments were carried out in order to get an idea about the toxicity of the substance — similar to the tests reported above. The results are given in Table 8.

TABLE 8.

Female Rats, 6 Months Old, Treated with Intraperitoneal Injection of Ethylene Thio-urea, given in Two Equal Doses on Two Successive Days.

Number of rats	Average weight	Dose	Died	Autopsy
5	213 g	20 mg	0	
5	210 g	200 mg	3	
5	222 g	300 mg	5	

Even though thio-urea is not so toxic as assumed at once and even though it is much easier and less expensive to prepare than thio-uracil, in view of the observations presented in this chapter it did not seem advisable to employ this substance clinically in cases of thyrotoxicosis. The same applies to ethylenethio-urea.

From the literature, thio-urea appears to have been employed for the treatment of thyrotoxicosis but to a very limited extent. In his first publication of this subject, in 1943, *Astwood*[15] states that this substance apparently is less toxic than thio-uracil. Subsequently *Astwood* (1944)[16] has turned to employ thio-uracil exclusively. Also *Paschkis et al.*[153], *Himsworth*[77, 78] and *Frisk*[55], who likewise used thio-urea at first, have later gone on to use thio-uracil — because of the great toxicity of thio-urea. Here in Denmark *Torben Andersen*[9] has reported a case of death after treatment with thio-urea, and has likewise stopped using this substance. Also *Espersen & Roholm*[44] advise against the clinical employment of this substance in thyrotoxicosis.

From the observations mentioned above, the following points are to be emphasized:

The strumogenic effect of thio-urea is somewhat smaller than that of thio-uracil, and its toxicity is considerably greater. In animals even rather small doses of the substance produce very serious by-effects. Several experimental animals (rats) appear to be hypersensitive to thio-urea. This substance has to be looked upon as unsuitable for clinical use in thyrotoxicosis.

Chapter V

EFFECT OF THIO-URACIL ON THE NORMAL THYROID GLAND

In rats, as mentioned, thio-uracil produces enlargement of the thyroid with hyperplasia of its parenchyma. These changes make their appearance very rapidly and may even attain very high degrees. On this account, rats are very suitable as experimental animals when the effect of thio-uracil on the thyroid weight and histological picture are to be studied.

The purpose of the experiments to be mentioned now was to investigate the effect of thio-uracil on the thyroid under varying experimental conditions and, if possible, to find certain guiding principles for the dosage of the substance at its therapeutic employment against thyrotoxicosis.

As it is very important in such experiments exactly to know the size of the dose, it was taken to be necessary to give the substance to the animal through the esophageal tube instead of giving it in a low concentration in the drinking water or food. Therefore, each single dose was given through the esophageal tube as a suspension in 1 ml water with addition of 5 % mucilage. As female rats of 6 months, weighing about 200 g, appeared particularly suitable for these experiments, such animals have been used in all these experiments, which were carried through with thio-uracil and methylthio-uracil. In this way a higher degree of certainty has been obtained with regard to the experimental results. At the same time, methylthio-uracil, which undoubtedly will find therapeutic employment, has been tried out rather thoroughly.

The animals were killed 24 hours after the last dose, having been weighed just before. On autopsy, immediately after the death

of the animal, the thyroid was removed at once weighed and prepared for histological examination — as described in Chapter II.

The effect of thio-uracil on the weight and histological picture of the thyroid was examined under the following, varying, experimental conditions:

1. Increasing dose of thio-uracil (1/4—80 mg daily) through a constant period.
2. Constant dose of thio-uracil for an increasing number of days (2—40 days).
3. Differing dosage (from 3 times daily to once every 3 days) through a constant period.
4. Effect on the thyroid from concluded effective treatment with thio-uracil.
5. Effect on the thyroid from protracted treatment with thio-uracil (6—7 months).

1. *Effect of Thio-uracil on the Thyroid, with Increasing Doses and Constant Period of Treatment.* (Thio-uracil and Methylthio-uracil.)

Experimental period: 15 days.

Doses employed: 1/4, 1/2, 1, 2 1/2, 5, 10, 20, 40 and 80 mg daily.

A. *Effect on the Thyroid Weight.*
Thio-uracil.

TABLE 9.

Female Rats, 6 Months Old, Treated with Thio-uracil for 15 Days.

Number of rats	Initial weight	Daily dose	Weight after treatment	Thyroid weight	μ
9	206 g	1/4 mg	213 g	15.9 mg	3.2
11	205 g	1/2 mg	206 g	15.6 mg	2.3
16	206 g	1 mg	203 g	21.8 mg	4.4
16	203 g	2 1/2 mg	207 g	27.0 mg	6.5
16	208 g	5 mg	207 g	24.9 mg	4.1
11	218 g	10 mg	220 g	27.4 mg	3.6
11	205 g	20 mg	215 g	34.4 mg	5.6
11	204 g	40 mg	203 g	38.7 mg	5.4
5	213 g	80 mg	208 g	41.9 mg	7.0

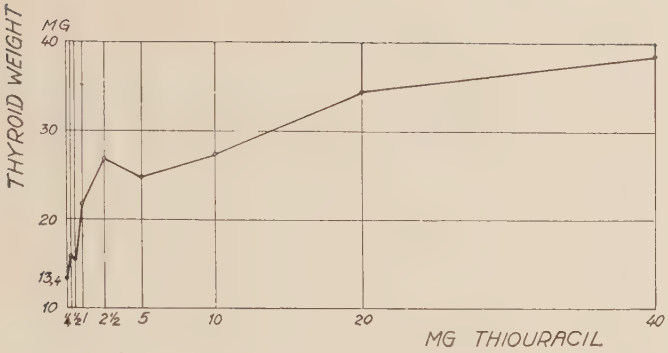


Fig. 4. Curve for the thyroid weight in female rats, 6 months old, treated with thio-uracil for 15 days.

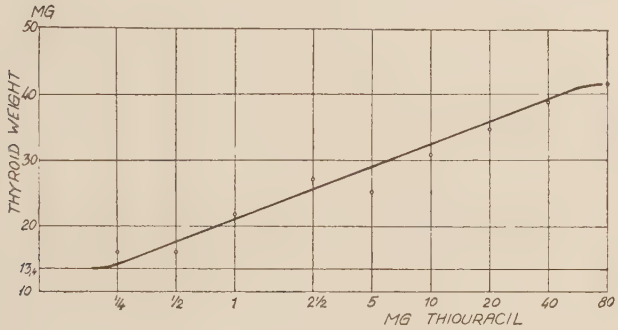


Fig. 5. Curve (*logarithmic*) for the thyroid weight in female rats, 6 months old, treated with thio-uracil for 15 days.

Methylthio-uracil.

TABLE 10.

Female Rats, 6 Months Old, Treated with Methylthio-uracil for 15 Days.

Number of rats	Initial weight	Daily dose	Weight after treatment	Thyroid weight	μ
10	205 g	1/4 mg	204 g	16.9 mg	2.7
11	205 g	1/2 mg	200 g	21.0 mg	4.5
10	204 g	1 mg	206 g	27.8 mg	3.3
11	206 g	2 1/2 mg	208 g	33.1 mg	8.3
11	214 g	5 mg	215 g	36.8 mg	8.5
10	203 g	10 mg	213 g	39.6 mg	6.7
11	205 g	20 mg	202 g	45.0 mg	8.2
11	204 g	40 mg	198 g	44.6 mg	9.7
6	211 g	80 mg	192 g	42.5 mg	13

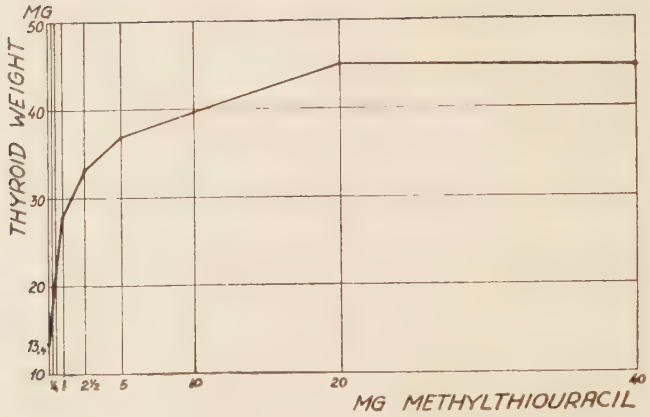


Fig. 6. Curve for the thyroid weight in female rats, 6 months old, treated with methylthio-uracil for 15 days.

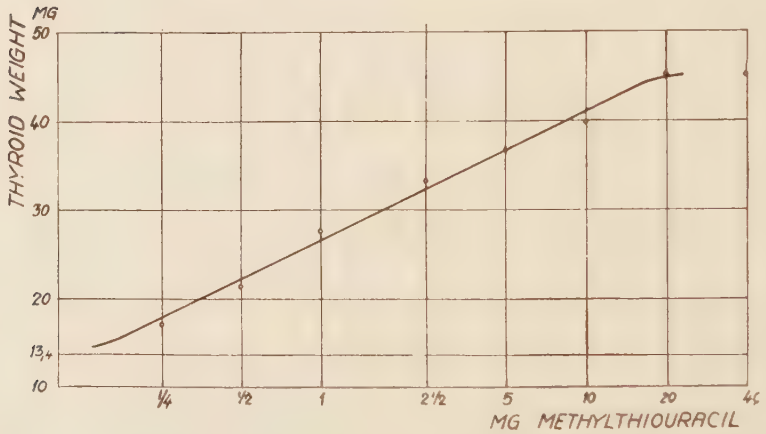


Fig. 7. Curve (*logarithmic*) for the thyroid weight in female rats, 6 months old, treated with methylthio-uracil for 15 days.

From Tables 9 and 10 and from Figs. 4—7 it is evident that methylthio-uracil has a far stronger strumogenic effect on rats than has thio-uracil. A daily dose of 20 mg methylthio-uracil for 15 days gives a maximal effect on the thyroid weight; and this effect is stronger than that obtained with a daily dose of 80 mg thio-uracil. Higher doses of methylthio-uracil give no additional effect on the thyroid, the weight of which appears even to

decrease, and the animals are now losing weight. These findings indicate a toxic effect, which with thio-uracil appears not to set in till the daily dose is raised to 80 mg. These findings correspond to the observation reported in Chapter IV: that thio-uracil is less toxic than methylthio-uracil.

The following points are to be emphasized:

1. Methylthio-uracil has a considerably stronger strumogenic effect than has thio-uracil.
2. When female rats, 6 months old, are treated with thio-uracil in doses increasing from 1/4 to 80 mg daily for 15 days, the thyroid weight increases after a straight line. Under the given experimental conditions the thyroid weight is a logarithmic function of the size of the dose.
3. When female rats of 6 months are treated with methylthio-uracil in increasing doses, from 1/4 to 20 mg daily for 15 days the thyroid weight increases after a straight line. Under the given experimental conditions the thyroid weight is a logarithmic function of the dose employed. Doses of 40 and 80 mg methylthio-uracil daily for 15 days give no additional increase in the thyroid weight.

B. *Effect on the Histological Picture of the Thyroid.*

Histological examination of the thyroid was performed on all the rats mentioned under section A.

When female rats of 6 months are treated with thio-uracil and methylthio-uracil in increasing doses, from 1/4 mg to 80 mg daily, for 15 days, the thyroid shows gradual histological changes corresponding to the gradual increase in its physiological activity. It is to be mentioned, however, that the physiological activity of the thyroid in these animals does not increase in spite of the histological signs of such an increase, and the reason for this is the specific effect of thio-uracil on the synthesis of the thyroid hormone (see Chapter X).

On this account it seemed more correct to adopt the designation histological activity instead of physiological activity. In the histological estimation of the thyroid, the following features are taken as criteria of histological activity:

1. Increase in the height of the epithelial cells, resulting in diminution of the follicular lumina.
2. Decrease in colloid — varying from marginal vacuolization and decoloration to complete loss of the colloid.
3. Increasing vascularization of the interfollicular connective tissue.

The histological features of the normal thyroid in untreated female rats of 6 months are mentioned in Chapter II, and it is pointed out that in the control animals we may meet with variations in the slight histological activity from one animal to another, and also from one section to another within the same gland. Similar variations may be observed in the increasing histological activity under treatment with thio-uracil, but on the whole there is a striking consistency of the histological pictures from animals under the same treatment. A measure for the increasing histological activity might be obtained, for instance, by calculation of the average height of the epithelial cells. Such examinations did not seem necessary, however, as the more rough estimation — by eye measurement — has proved quite sufficient. The following procedure was adopted:

A close comparison is made between the histological pictures of the thyroids from animals that have received the same treatment. Four sections have been stained from each thyroid. The two sections most characteristic of the group are picked out; and they are used for the comparative examination of the histological activity from one group of animals to another.

Results.

On histological activation of the thyroid under the treatment with thio-uracil and methylthio-uracil, the above-mentioned signs of histological activity make their appearance in the following sequence:

1) increase in the height of the epithelial cells,
2) decrease in colloid, and
3) increased vascularization.

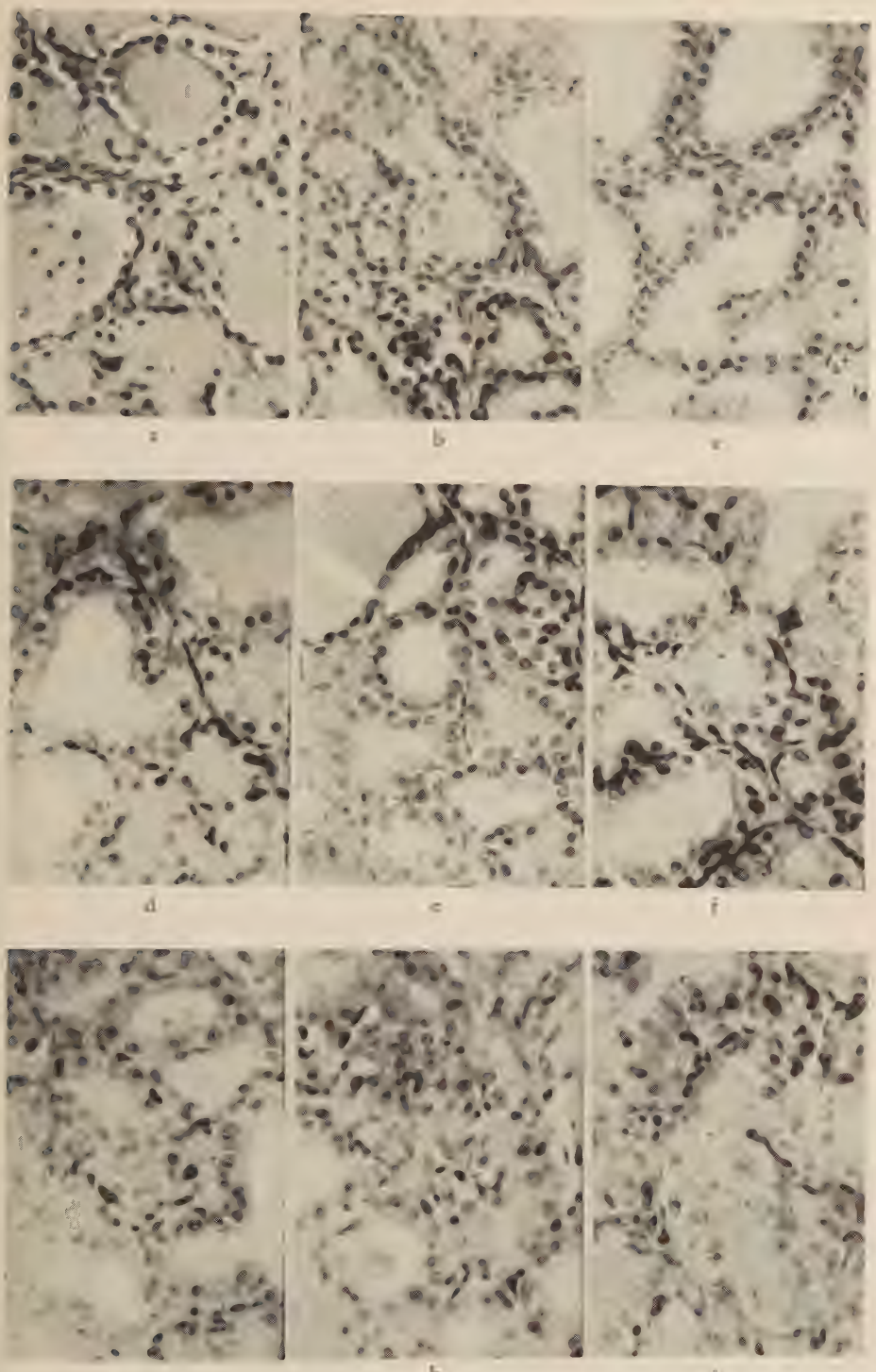


Fig. 8 Microphotos of thyroids from female rats, treated respectively with ¼ (a), ½ (b), 1 (c), 2½ (d), 5 (e), 10 (f), 20 (g), 40 (h), and 80 (i) mg thio-uracil daily for 15 days (Magnif. × 400.)

Thio-uracil.

The results are evident from Fig. 8.

Even after treatment with 1/4 or 1/2 mg thio-uracil for 15 days, distinct, although weak, signs of histological activity are seen. After this, there will be noticed a gradual increase in the histological activity, which reaches its maximum at the dose of 80 mg at which dosage the signs of histological activity are extreme.

Methylthio-uracil.

As methylthio-uracil has a far stronger strumogenic effect than has thio-uracil, even the dose of a 1/4 mg gives quite considerable signs of histological activity (marked increase in the height of the cells and pronounced marginal vacuolization). The changes here correspond very well to those obtained on treatment with 1 mg thio-uracil.

Owing to the stronger effect of methylthio-uracil, the difference in the histological activity from one group to another is less pronounced. A dosage of 20 mg daily gives about a maximal effect. The same picture is seen after 40 mg as efter 20 mg. After 80 mg the signs of histological activity are a little more pronounced than after 20 mg.

Briefly, these studies have shown the following features:

Histological examination of the thyroid of female rats, 6 months old, treated with thio-uracil in increasing doses — from 1/4 mg to 80 mg daily — for 15 days, shows a gradual increase in the histological activity, from slight activity (1/4 mg) to maximal activity (80 mg).

Similar tests with methylthio-uracil show than even 1/4 mg induces pronounced signs of activity, and that 20 mg practically gives a maximal effect. Further increase in the dose gives no particular rise in the histological activity.

Given in relatively low doses, methylthio-uracil has a far stronger effect on the histological picture of the thyroid than has thio-uracil.

The results recorded under A and B show that there is a very good concordance between the thio-uracil effect on the weight of

the thyroid and the histological picture of the gland on treatment with increasing doses through a constant period.

2. *Effect of a Constant Dose given for an Increasing Number of Days.* (Thio-uracil and Methylthio-uracil).
Doses employed: Thio-uracil, 10 mg daily;
methylthio-uracil, 5 mg daily.

The following experimental periods were employed: 2 — 5 — 10 — 15 — 20 and 40 days.

The effect on the thyroid weight with increasing periods of treatment is evident from Tables 11 and 12 and from Figs. 9, 10, 11 and 12.

A. *Effect on the Thyroid Weight.*
Thio-uracil.

TABLE 11.

Female Rats, 6 Months Old, Treated with 10 mg Thio-uracil Daily.

Number of rats	Initial weight	Duration of treatment	Weight after treatment	Thyroid weight	μ
5	203 g	2 days	205 g	13.7 mg	1.7
5	219 g	5 days	231 g	21.5 mg	2.0
7	222 g	10 days	212 g	24.8 mg	4.4
11	218 g	15 days	220 g	27.4 mg	3.6
14	203 g	20 days	209 g	28.4 mg	5.2
7	205 g	40 days	212 g	31.8 mg	7.9

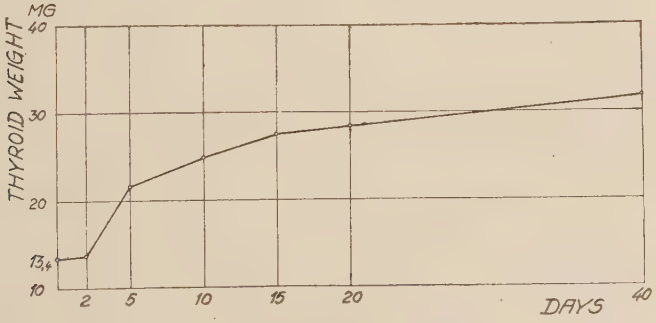


Fig. 9. Curve for the thyroid weight in female rats, 6 months old, treated with 10 mg thio-uracil daily.

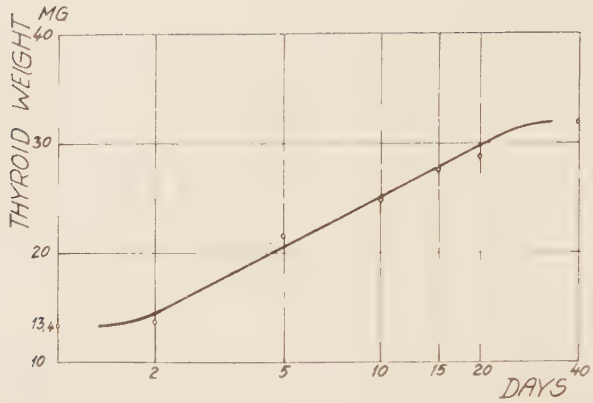


Fig. 10. Curve (*logarithmic*) for the thyroid weight in female rats, 6 months old, treated with 10 mg thio-uracil daily.

Methylthio-uracil.

TABLE 12.

Female Rats, 6 Months Old, Treated with 5 mg Methylthio-uracil Daily.

Number of rats	Initial weight	Duration of treatment	Weight after treatment	Thyroid weight	μ
5	200 g	2 days	198 g	12.9 mg	2.0
5	226 g	5 days	227 g	22.2 mg	3.0
5	228 g	10 days	233 g	32.1 mg	6.8
11	214 g	15 days	215 g	36.8 mg	8.5
5	201 g	20 days	214 g	38.2 mg	8.8
6	203 g	40 days	216 g	41.3 mg	8.5

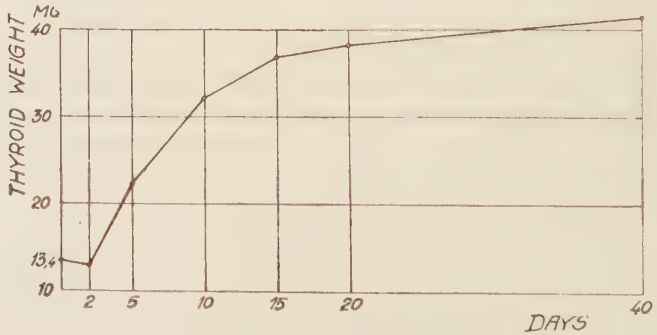


Fig. 11. Curve for the thyroid weight in female rats, 6 months old, treated with 5 mg methylthio-uracil daily.

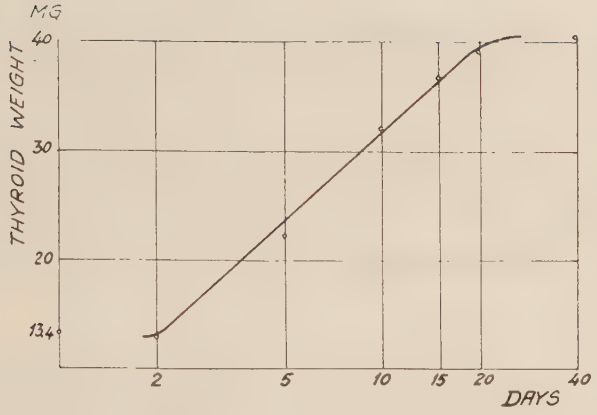


Fig. 12. Curve (*logarithmic*) for the thyroid weight in female rats, 6 months old, treated with 5 mg methylthio-uracil daily.

These experiments gave the following results:

Methylthio-uracil has a strumogenic effect which is much stronger than that of thio-uracil. Although in the above-mentioned experiments thio-uracil was given in doses twice as large as those of methylthio-uracil, its strumogenic effect was considerably smaller. When female rats of 6 months were treated with 10 mg thio-uracil daily, the thyroid weight increased, after a couple of days, along a straight line until about the 20' day, and then the increase declined. Under the given experimental conditions the thyroid weight within this period behaves like a logarithmic function of the duration of the treatment.

Something similar was seen on treatment with 5 mg methylthio-uracil daily under otherwise uniform experimental conditions.

Further, it will be noticed that treatment for 15 days gives an almost maximal effect from thio-uracil as well as methylthio-uracil in the doses mentioned. Treatment with 10 mg thio-uracil or 5 mg methylthio-uracil daily for 2 days causes no increase in the thyroid weight.

B. *Effect on the Histological Picture of the Thyroid.*

What has been said in this chapter — section 1 B — concerning the estimation of the histological preparations applies also to the experiments mentioned in this section.

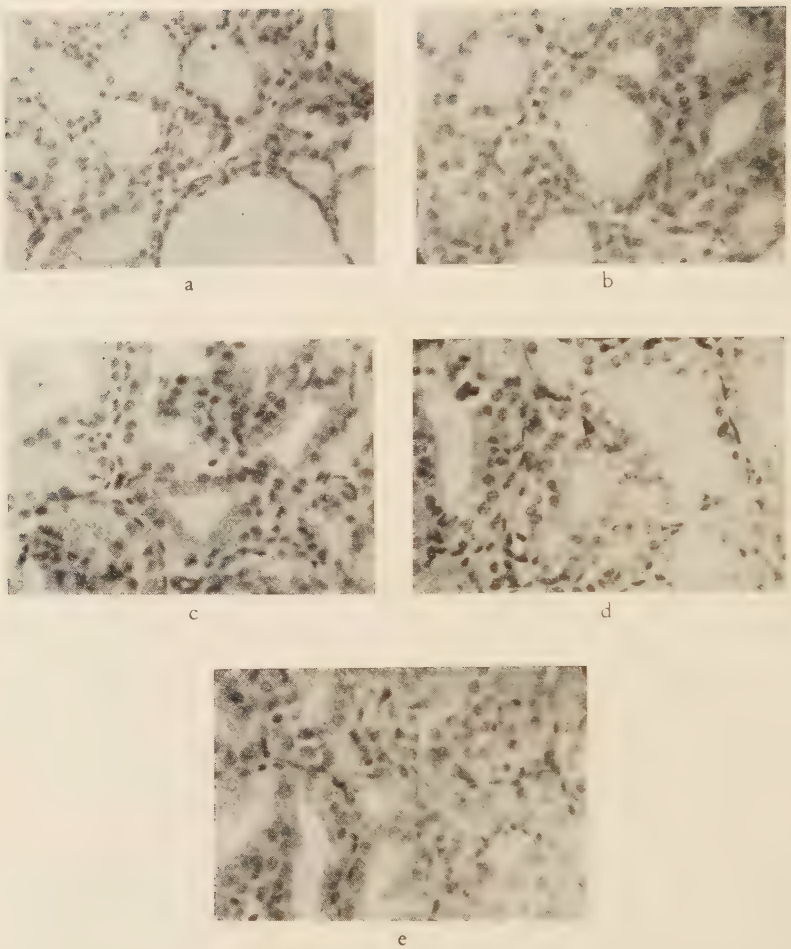


Fig. 13. Microphotos of thyroids from female rats, treated with 10 mg thio-uracil daily for respectively 2 (a), 5 (b), 10 (c), 20 (d), and 40 (e) days. (Magnif. × 400.)

Results.

The histological results from treatment of female rats of 6 months with 10 mg thio-uracil daily for an increasing number of days — from 2 to 40 days — are illustrated in Fig.13.

After 2 days' treatment there are slight, but distinct, signs of increased histological activity. After 40 days the histological

activity is very pronounced. Between these two extremes — 2—40 days' treatment — the histological activity is seen to increase gradually.

After treatment with 5 mg methylthio-uracil daily for 2—40 days there is likewise a gradual increase in the histological activity of the thyroid. But this is considerably more pronounced after 5 mg methylthio-uracil for 2 days than after 10 mg thio-uracil for 2 days. The same applies to the appearance of the gland after treatment for 40 days. Also under treatment with methylthio-uracil it takes 40 days before the maximal effect appears.

On treatment of female rats of 6 months with 10 mg thio-uracil or 5 mg methylthio-uracil daily for 2—40 days the thyroid shows a gradually increasing histological activity. On comparison of these results with the effect of the treatment on the thyroid weight (in the same animals) the signs of histological activity are found to appear earlier than the increase in weight. Otherwise there is good agreement between the effect of the treatment on the thyroid weight and on the histological features of the gland.

3. *Effect of Thio-uracil with Varying Dosage.*

Besides by oral administration, the thio-uracil effect on the thyroid of the rat may be produced also by subcutaneous injection (see p. 31) and by intraperitoneal injection (see p. 68).

It is reasonable to think that the substance is active also on other forms of administration (*e. g.*, intramuscular and intravenous). For clinical use, however, the oral administration is most important, and hence it has been used exclusively in the experiments to be mentioned here.

These experiments were performed with a view to the adjustment of the clinical dosage of thio-uracil in cases of thyrotoxicosis, aiming to estimate the effect of thio-uracil on the thyroid weight and the histological picture of the gland on varying oral dosage of the substance.

The dosages here employed are recorded in Tables 13 and 14 and in Figs. 14 and 15, in which also the effect of the treatment on the thyroid weight and histological picture can be read directly. The experiments were performed on female rats, 6 months old.

In all the experiments each single dose was given through an esophageal tube, the remedy being suspended in 1 ml water with an addition of 5 % mucilage. In those experiments where two doses were given on one day, the first was given at 8—9 a. m., the second at 4—5 p. m. When three doses were given on one day, one was given at noon. In the estimation of the histological picture, the same procedure was employed as described on p. 34. Transitional forms are designated as (+).

TABLE 13.

Female Rats, 6 Months Old, Treated with Thio-uracil for 15 days.

No. of rats	Initial weight	Dosage	Weight after treatment	Thyroid weight	μ	Histological activity
7	205 g	3.33 mg 3 × daily	200 g	32.6 mg	3.1	+++
6	208 g	5 mg 2 × daily	216 g	31.1 mg	4.1	+++
11	218 g	10 mg daily	220 g	27.4 mg	3.6	+++
5	208 g	10 mg every 2' day	215 g	20.0 mg	3.0	+(+)
5	206 g	20 mg every 2' day	215 g	20.3 mg	1.8	++
5	209 g	10 mg every 3' day	214 g	17.7 mg	1.9	+
5	208 g	30 mg every 3' day	219 g	19.8 mg	6.8	+(+)

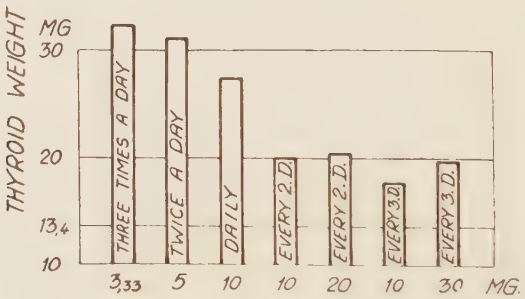


Fig. 14. Thyroid weight in female rats, 6 months old, treated with thio-uracil for 15 days.

Here, as in the preceding section of this chapter, there is a rather close concordance between the changes in the thyroid weight and the histological activity. Within the first three groups in each schematic presentation the changes in the histological picture were only small.

TABLE 14.

Female Rats, 6 Months Old, Treated with Methylthio-uracil for 15 Days.

No. of rats	Initial weight	Dosage	Weight after treatment	Thyroid weight	μ	Histological activity
7	207 g	1.67 mg 3 × daily	204 g	37.9 mg	6.6	+++
5	206 g	2.5 mg 2 × daily	221 g	36.3 mg	2.5	+++
11	214 g	5 mg daily	217 g	36.8 mg	8.5	+++
10	217 g	5 mg every 2' day	219 g	21.9 mg	5.0	++
11	208 g	10 mg every 2' day	208 g	23.8 mg	4.3	++(+)
5	227 g	5 mg every 3' day	235 g	17.4 mg	2.9	+
5	206 g	15 mg every 3' day	214 g	19.1 mg	1.7	++

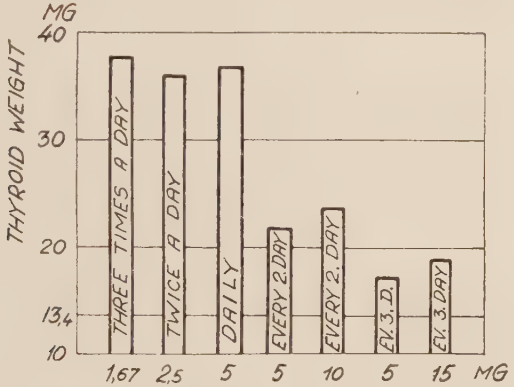


Fig. 15. Thyroid weight in female rats, 6 months old, treated with methylthio-uracil for 15 days.

The treatment of female rats, 6 months old, with 10 mg thio-uracil daily, distributed on respectively 1, 2 and 3 daily doses, shows that the thio-uracil effect on the thyroid weight increases when the same total dose is distributed on more doses in the course of the day.

In the experiments carried out with methylthio-uracil these changes were not very pronounced. Only when the daily total dose was distributed over 3 daily doses, was a greater effect observed than when this total dosage was given at once. Probably this is due to the very strong strumogenic effect of methylthio-uracil. This substance has such a strong immediate effect on the thyroid

that even 5 mg given once a day for 15 days brings about almost the maximal weight increase and histological activity of which the thyroid is able within this length of time.

When 10 mg thio-uracil and 5 mg methylthio-uracil, instead of being given as a daily dose, are given as a single dose every other or third day, the effect is reduced quite considerably — a reduction that can be altered but little by doubling or trebling of the dose. These findings indicate a rather rapid excretion of the substances.

So the treatment of rats of 6 months with thio-uracil and methylthio-uracil for 15 days with varying oral dosage shows that the effect of thio-uracil upon the thyroid increases only in a slight degree when the daily total dose is distributed over several single doses in the course of the day. On the other hand, the thio-uracil effect decreases quite considerably when the same total dose is given as single doses every other or every third day.

4. *Effect on the Thyroid from Concluded. Effective Treatment with Thio-uracil.*

In the preceding section of this chapter it has been demonstrated that the thio-uracil effect on the thyroid of the rat appears rapidly. Thus, even in 2 days the effect of 5 mg methylthio-uracil can be recognized distinctly on histological examination of the glands, whereas at this point of time there is not yet any increase in the thyroid weight. After 15 days of treatment, a strong effect is seen on the thyroid weight as well as on the histological feature.

Even though thio-uracil is excreted rather rapidly from the organism (see Chapter VIII) its effect on the thyroid subsides slowly. Thus, on intraperitoneal injection into female rats of 6 months of respectively 30 and 100 mg thio-uracil and methylthio-uracil for 2 days (toxicity experiments), a slight though definite enlargement of the thyroid was seen as long as 17 days after the last injection. In all the experiments the average thyroid weight was between 16.1 and 17.3 mg (N.B. No difference after treatment with 60 and 200 mg). After 20 mg, however, no increase was seen in the weight (13.1—13.5 mg).

The continued influence of the thio-uracil effect upon the

thyroid weight and the histological features of the gland after discontinuance of the treatment was examined further in the following experiments:

Female rats, 6 months old, were treated with 5 mg methylthio-uracil daily given through an esophageal tube, for 15 days. The animals were killed in groups, respectively 0, 5, 10, 20, 40 and 80 days after the discontinuance of the treatment. On all the animals, autopsy was performed, and the thyroid was removed, weighed and examined histologically (in the usual manner). For examination of the histological picture, the same procedure was employed as described on p. 34. In the account of these experiments too, transitional forms are designated by means of (+). The results are recorded in Table 15 and Figs. 16—17.

TABLE 15.

Female Rats, 6 Months Old, Treated with 5 mg Methylthio-uracil for 15 Days.

No. of rats	Initial weight	No. of days after end of treatment	Weight at end of treatment	Thyroid weight	μ	Histological activity
11	214 g	0 days	215 g	36.8 mg	8.5	+++
5	210 g	5 days	194 g	24.9 mg	3.4	++(+)
6	208 g	10 days	194 g	21.1 mg	3.8	+
6	209 g	20 days	202 g	17.0 mg	3.2	(+)
5	212 g	40 days	194 g	22.1 mg	2.0	(+)
6	213 g	80 days	198 g	25.4 mg	7.1	+

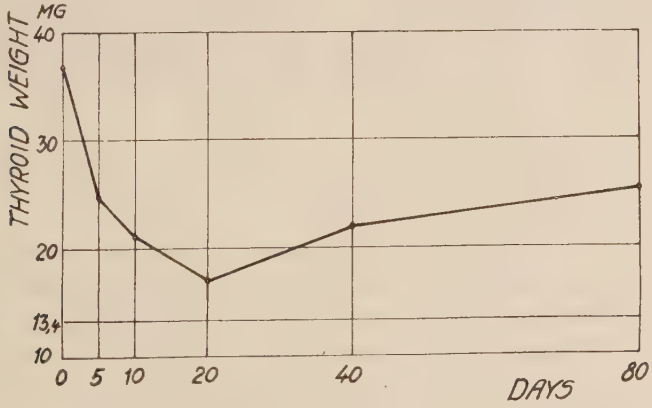


Fig. 16. Curve for the thyroid weight in female rats, 6 months old, *after* treatment with 5 mg methylthio-uracil for 15 days.

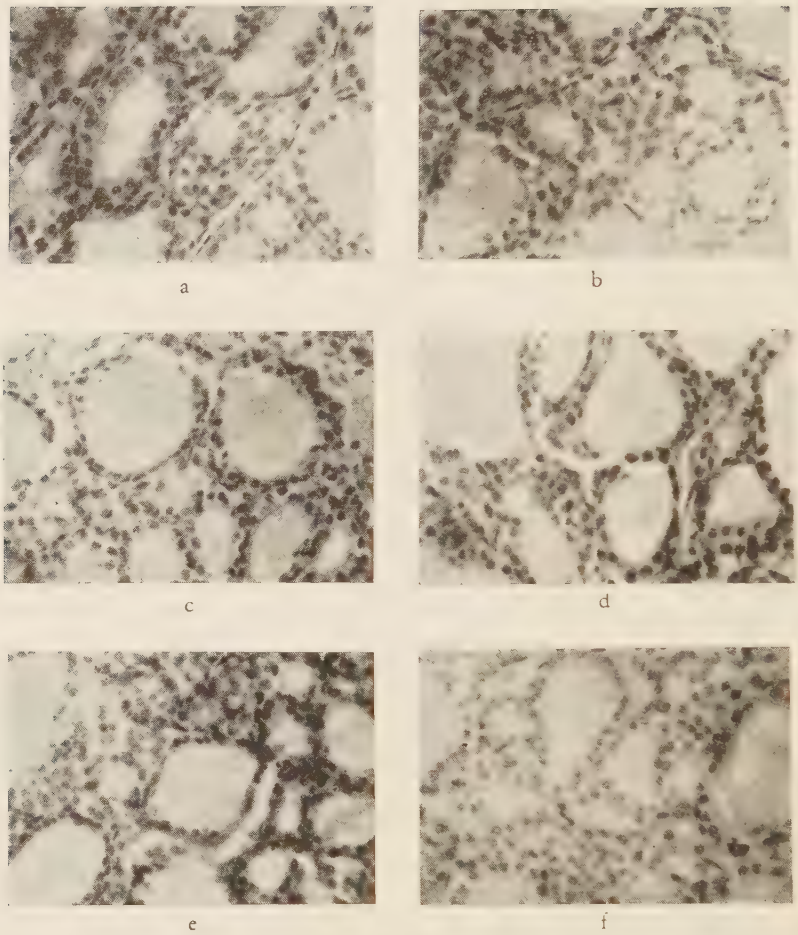


Fig. 17. Microphotos of thyroid from female rats respectively 5 (a), 10 (b), 20 (c), 40 (d), and 80 (e, f) days *after* treatment with 5 mg methylthio-uracil for 15 days (cf. Fig. 31, a). (Magnif. × 400.)

After conclusion of the treatment of female rats, 6 months old, with 5 mg methylthio-uracil daily for 15 days, the thyroid weight falls rapidly, and within about 20 days it reaches a value only a little above that for the controls.

In keeping with this the signs of histological activity decrease as follows:

After 5 days: Picture of great activity, but with commencing colloid formation.

After 10 days: Marked decrease in the height of epithelial cells; follicles filled with faintly colored colloid, and showing pronounced marginal vacuolization.

After 20 and 40 days: Height of cells normal or moderately increased. Colloid staining more deeply, though with some marginal vacuolization.

After 80 days: Some sections show similar findings as after 20 and 40 days; others show considerable activity, with pronounced increase in the height of the cells and loss of colloid.

After a few weeks there is a secondary rise in the thyroid weight, which 80 days after discontinuance of the treatment has reached a value about twice as great as the thyroid weight in the controls. At the same time, the histological examination shows that after 80 days there appeared to be an increase in the histological activity of the thyroid.

Here as elsewhere, we meet with a certain degree of variation in the histological features from one animal to another within the same group, and from one section to another from the same gland. Some thyroids (80 days after the discontinuance of the treatment), however, show marked signs of histological activity (see Fig. 17, f) that have never been encountered in the controls.

Briefly, these experiments have shown the following features:

After treatment with 5 mg methylthio-uracil daily for 15 days, female rats of 6 months show after discontinuance of the treatment a fall in the thyroid weight accompanied by decreasing histological activity. After a few months, however, there is a secondary rise in the thyroid weight, and at the same time some slight or moderate signs of histological activity are seen in the thyroid, *i. e.*, a secondary histological activation.

In the following chapter, these observations will be mentioned further, in connection with determination of the metabolism under the same experimental conditions.

5. *Effect on the Thyroid of Rats from Protracted Subcutaneous Injection of Thio-uracil.*

The thio-uracil effect on the weight and histological picture of the thyroid after treatment for up to 40 days has been described in section 2 of this chapter. It has been shown that 10 mg thio-uracil and 5 mg methylthio-uracil within this length of time give a quite considerable increase in the thyroid weight and almost extreme hyperplasia of the specific parenchyma. The purpose of the experiments mentioned here was to see whether the thyroid function would remain inhibited even under protracted thio-uracil treatment or whether the thyroid would be able somehow to overcome — entirely or in part — the inhibitory effect from the remedy and restore normal conditions in the organism. Naturally this question is of the very greatest importance to the employment of thio-uracil in clinical medicine. The following experiment was carried out with employment of 25 female rats and 25 males of the same age.

From each group, 5 animals were used as controls and, thus, given no treatment. The remaining 40 animals (20 females and 20 males) were treated with thio-uracil from their 12' day of life to the 205' day. As it is very difficult to give such small rats the remedy through an esophageal tube, it was decided to employ subcutaneous administration — the more so as this method of administration had proved to give a greater thio-uracil effect than the peroral method (see p. 31). Throughout the experiment the single doses were injected subcutaneously on the back, suspended in ½ ml 0.9 % NaCl. In order to spare the animals as far as possible, throughout the experimental period they were given only 1 dose 3 times a week (every Monday, Wednesday and Friday). With the growth of the animals the size of the dose was increased after the following scale.

1'	week	of	treatment:	1	mg	thio-uracil	per	injection		
2'	—	-	—	4	-	—	-	—		
3'—8'	—	-	—	5	-	—	-	—		
9'—29'	—	-	—	10	-	—	-	—		

The experiment lasted altogether 205 days (females, 204 days; males, 206 days).

In order to make sure that subcutaneous injection of the remedy on every other day would have a noticeable antithyroid effect, the following experiment (recorded in Table 16) was carried out. From Table 16 it will be noticed that, with the dosage here employed, thio-uracil has a pronounced effect on the thyroid.

TABLE 16.

Female and Male Rats, 6 Months Old, Treated with Subcutaneous Thio-uracil for 15 Days.

No. of rats	Sex	Initial weight	Dosage	Weight after treatment	Thyroid weight	μ
6	F.	216 g	10 mg every 2' day	218 g	26.7 mg	3.6
6	M.	213 g	10 mg every 2' day	239 g	26.9 mg	7.2

Results.

Thyroid Weight.

TABLE 17.

Body Weight and Thyroid Weight in Rats Treated with Thio-uracil (subcutaneously) from the 12' to 205' Day of Life. Control Animals Entered for Comparison.

Number of rats	Sex	Initial weight	Weight after treatment	Thyroid weight	μ
20	F.	24 g	187 g	49.4 mg	9.2
5 (controls)	F.	29 g	186 g	13.9 mg	1.0
20	M.	23 g	285 g	71.8 mg	2.2
5 (controls)	M.	21 g	282 g	14.3 mg	0.8

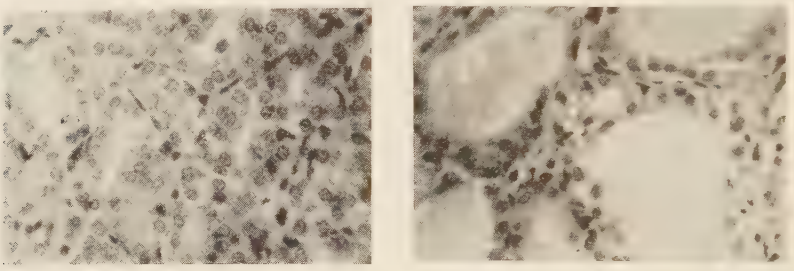
From Table 17 it will be noticed that female and male rats exposed to the action of a relatively slight dose of thio-uracil from the 12' to the 205' days of life develop a very considerable goiter. The great difference in the average thyroid weight for the females

and males disappears when the thyroid weight is calculated per 200 g rat, being then:

Females: 52.8 mg/200 g.
Males: 50.4 mg/200 g.

Histological Picture of the Thyroid.

On histological examination, all the thyroid preparations from the treated animals here recorded showed signs of marked histological activity. Here too we meet with noticeable variations in



a b

Fig. 18. Microphotos of thyroids from a female rat (a) and a male rat (b), treated with thio-uracil from the 12' to 216' day of life (see the text). (Magnif. × 400.)

the histological picture from one animal to another, in the males as well as in the females (Fig. 18).

In some specimens we thus meet with a considerable number of follicles filled with colloid, while at the same time there is a distinct increase in the height of the epithelial cells and in the vascularization of the interfollicular connective tissue. On the other hand, other specimens show evidence of extreme hyperplasia. Here the increased height of the cells and the vascularization are very pronounced, and the lumina of the follicles are very small and contain no colloid. The two pictures here described, as illustrated by Fig. 18 a and b, constitute the extreme limits, between which all sorts of transitions are found. In every specimen the interfollicular connective tissue is slightly increased.

The fact that some of the specimens show several follicles filled with colloid and, at the same time, evidence of marked histological

activity, by no means signifies that the thyroid is about getting over the antithyroid effect of thio-uracil. For one thing, such a claim would have to be based on determination of the thyroid hormone content of the colloid. Even though such a determination might give normal values, in the present experiments this finding could be quite compatible with a continued and undiminished antithyroid effect, as the dose here employed has merely a moderate antithyroid effect on the thyroid gland (cf. the experiments of brief duration — 15 days — with 10 mg thio-uracil every other day). So these experiments have given the following findings:

On exposure of female and male rats to a moderate thio-uracil effect from their 12' to their 205' days of life, the thyroid weight increases very markedly.

In comparison with the controls, this rise in the thyroid weight amounts to about 350 % for the females, about 500 % for the males.

At the same time, the histological picture of the thyroid shows evidence of pronounced or even extreme histological activity.

These experiments have offered no evidence in support of the idea that under protracted treatment the thyroid is able to overcome the antithyroid effect of thio-uracil.

Discussion.

In the literature accessible to the writer, only rather limited investigations have been reported on the thio-uracil effect upon the normal thyroid gland — similar to the experiments recorded in this chapter. On the whole, a comparison between the results obtained by the various authors shows a fairly high degree of concordance. *Mackenzie & Mackenzie*[119, 121] carried out experiments with sulfaguanidine, which has a somewhat weaker strumogenic effect than has thio-uracil. In keeping with the results recorded in this chapter, the two investigators found the thyroid weight in rats to rise after a straight line within the first two weeks on increasing concentration of the sulfaguanidine content of the diet. They state that the thyroid weight is directly propor-

tional to the sulfaguanidine concentration of the food and of the blood, and that the increase of the thyroid weight roughly corresponds to an increase of 10 mg above the normal for 1 % addition of the substance. Furthermore, these authors find the rise in thyroid weight to be a logarithmic function of the time.

Moreover, *Mackenzie & Mackenzie*[121] find the increase in thyroid weight to be associated with evidence of increasing activity in the histological picture of the gland. These changes, which appear to reach the maximum in 2 weeks, are recognizable as early as after 2—4 days' treatment. After 2 days of treatment, however, these authors have been able to demonstrate an increase of the thyroid weight to 35 % above the normal. The findings recorded by these authors do not quite correspond to the experimental results reported in this chapter, which just show the histological changes to make their appearance prior to the increase in weight — a result, which also *Freiesleben et al.*[53] arrived at. Indeed, *Mackenzie & Mackenzie*[121] state that the histological changes appear at a lower concentration of the remedy than does the increase in thyroid weight; and they assert that it is not justifiable from the size of the thyroid to draw any conclusion as to the degree of hyperplasia or lack of colloid. This, of course, is correct if the experimental conditions are not known.

Williams, Weinglass et al[205] say that the histological activity of the thyroid is consistent with its increase in weight, but this does not apply to its colloid content.

My own experiments have shown that on brief activation of the thyroid there is a strikingly marked conformity between the increase in the weight of the thyroid and its histological activity, including also its loss of colloid, whereas in more protracted experiments the marked goiter formation and histological activity appear to be associated with the tendency to colloid formation — something that has been observed also by *Kennedy & Purves*[95] in their experiments with rape seeds, which contain a derivative of thio-urea. It may be, however, that this tendency to colloid formation is due to the circumstance that the inhibitory effect upon the thyroid from the dose employed is incomplete, and that at the same time it becomes relatively diminished, as the thyroid in-

creases in weight and the follicles become more numerous. Thus, a dose of thio-uracil that is able completely to inhibit the thyroid function in a young rat, will not continuously be capable of this as the animal grows up.

My experiments have shown that after discontinuance of the thio-uracil treatment the thyroid weight in rats soon falls off without becoming quite normal — just as the signs of histological activity subside. Similar results have been obtained by *Mackenzie & Mackenzie*[121], besides by *Freiesleben et al.*[53] The former authors state that the thyroid weight had not yet become normal as long as 4 weeks after the discontinuance of the treatment, and they think that this is attributable to the presence of new follicles.

Freiesleben et al.[53] found the thyroid weight to be slightly increased as long as 50 and 100 days after the discontinuance of the treatment whereas the histological changes have subsided completely.

My own experiments have shown, however, that a secondary rise in the thyroid weight may appear after 80 days, and also that there is a tendency to secondary activation of the histological picture. These findings have not yet been confirmed by other investigators; and they are difficult to explain. In the following chapter they will be discussed further, in connection with determinations of the metabolism, which in keeping herewith shows a secondary fall in the rate of metabolism under the same experimental conditions.

Finally, it is to mentioned that *Freiesleben et al*[53] have been able to show that the mitochondria normally situated luminally in the cell were found after treatment with methylthio-uracil to be scattered throughout the hypertrophic cell.

In Part II, Chapter V, in which the dosage of thio-uracil and methylthio-uracil in cases of thyrotoxicosis is discussed in detail, the practical significance of the results reported in this chapter will be mentioned.

Chapter VI

EFFECT OF THIO-URACIL ON THE METABOLISM

The most important effect of thio-uracil on the organism is its influence on the production of thyroid hormone. How this effect is brought about will be mentioned elsewhere. The action of thio-uracil results in a decrease in the amount of thyroid hormone in the organism. This, in turn, will cause a fall in the oxygen consumption and in the carbon dioxide output, that is, a fall in the metabolism of the organism. At the same time, a state of hypothyroidism begins to develop, even though it takes a considerable length of time before this manifests itself in objectively recognizable changes.

By determination of the oxygen consumption in animals under treatment with thio-uracil we have an expression of the cellular function of the organism and thus for the hypothyroid state. So determination of the metabolism of the animal gives us direct information about the hormonal function of the thyroid. The deviations from the normal are ascertained by comparison of the metabolic results obtained from treated animals and controls, which — apart from the thio-uracil treatment — are kept under identical experimental conditions.

In this chapter the thio-uracil effect on the metabolism of the rat under varying experimental conditions will be investigated.

Experimental Animals.

For determination of the thio-uracil effect upon the weight of the thyroid and its histological features, female rats, 6 months old, were employed. For determination of the metabolism, I likewise have employed female rats of the same age and weight,

because in this way there will also be a possibility for comparison of the thio-uracil effect on these three biological aspects (the weight of the thyroid, its histology and the metabolism of the animal) under quite uniform experimental conditions.

The guinea-pig is the animal most suitable for the determination of the metabolism because the calmness — if not sluggishness — that characterizes this animal is a property that is of great value in determinations of the metabolism. As the guinea-pig does not react to the treatment with thio-uracil, however, at any rate not within fairly short experimental periods, it is not suitable for the present investigations. Therefore, as mentioned above, female rats of 6 months, weighing about 200 g, have been employed for all the determinations of the metabolism.

Rats are very lively animals, it is true, but this character can be eliminated for one or two hours by giving immediately before the determination of the metabolism an intraperitoneal injection of 62.5 mg urethane (1/4 ml of a 25 % aqueous solution). This gives soon a slightly narcotic — but otherwise quite harmless — effect on the rat, which, without falling asleep, keeps very quiet during the determination of the metabolism. It is to be emphasized that urethane has no effect on the respiration or circulation. Experiments with various doses of urethane have shown that 62.5 mg injected intraperitoneally is highly suitable for the purpose. This procedure has been employed in all the determinations of the metabolism.

Technique.

The metabolism was determined with the employment of the apparatus given by Marie Krogh. The experimental period has been 35—45 min., and prior to the experiments all the animals had fasted for 16—20 hours. The oxygen consumption is calculated after the curve in the usual manner, with regard being paid to the room temperature, atmospheric pressure and degree of moisture. After this, the obtained values give the amount of oxygen consumed in ml per min. and m^2 surface.

The experiments were carried out with employment of methyl-thio-uracil, which acts like thio-uracil but is considerably stronger.

The dose employed was given to the animals, through an esophageal tube, once daily, suspended in 1 ml water with an addition of 5 % mucilage.

Control Determinations.

In order to obtain a measure for the average metabolism in the animals here employed, altogether 141 determinations of the basal metabolism were first carried out on a total of 30 rats. The results of these determinations are recorded in Table 18.

TABLE 18.

141 Metabolism Determinations (Basal Metabolism) on 30 Untreated, Fasting, Female Rats, 6 Months Old (Weight about 200 g).

Rat. No.	Metab-olism	Rat No.	Metab-olism	Rat No.	Metab-olism	Rat No.	Metab-olism
1022.	123		89		101		99
	127		87		103	1042.	143
	114		87		101		132
	119	1029.	96		92		113
	110		93	1035.	108		100
	99		114		117	1043.	129
	104		121		111		101
1023.	101	1030.	98		102	1044.	104
	116		97		97		120
	114		143	1036.	124		102
	89		95		121	1045.	117
	109		115		136		119
1024.	98	1031.	123	1037.	122	1046.	109
	114		118		112		116
	97		102		94		134
	94		119		122		108
	100		109		97		86
	132		104	1038.	120	1047.	118
1025.	108		121		111		115
	154		113		98		119
	116	1032.	111		110		104
	119		103		97		104
	112		91	1039.	104	1048.	126
	112		99		109		131
1026.	108		88		115		125
	119		99		115		118

Rat. No.	Metab-olism	Rat No.	Metab-olism	Rat No.	Metab-olism	Rat No.	Metab-olism
	111		85		103		96
	120	1033.	103	1040.	111	1049.	126
1027.	111		113		128		144
	98		106		125		106
	115		114		104	1050.	137
1028.	95		111		118		125
	93		104	1041.	111		114
	89	1034.	115		105	1051.	116
	112		88		110		104
	94						

Average value: 110 (O_2 consumption in ml per min. and m^2 surface).

From Table 18 it is evident that the average basal metabolism in these 30 control animals is 110 ml oxygen/min., m^2 surface. This value is used as measurement of the normal metabolism of the experimental animals under complete fasting. For comparison, it is to be mentioned that *Christensen*[33], who likewise worked with female rats weighing 200 g, found the normal basal metabolism for these animals to average 109 ml O_2/min., m^2.

In the experiments reported below the metabolism will be mentioned in particular under the following conditions:

1. Metabolism on treatment with increasing doses of methylthio-uracil daily for 15 days (metabolism and size of dose).
2. Metabolism on treatment with 5 mg methylthio-uracil daily for an increasing number of days (metabolism and duration of treatment).
3. Metabolism *after* 15 days' treatment with 5 mg methylthio-uracil daily.

1. *Metabolism and Size of Dose (Methylthio-uracil).*

Experimental period: 15 days.

Doses employed: 1, 5, 20 and 40 mg daily.

The results of the metabolism determinations are recorded in Table 19 and Figs. 19 and 20.

The thyroid weights of the animals are entered at the same time as the metabolic results.

TABLE 19.

Metabolism Determinations on Female Rats, 6 Months Old, after Treatment with Methylthio-uracil for 15 Days.

No. of rats	Initial weight	Daily dose	Weight after treatment	Thyroid weight	Metabolism	μ
5	203 g	1 mg	191 g	23.4 mg	108	7
6	203 g	5 mg	194 g	31.7 mg	97	7
6	202 g	20 mg	185 g	38.9 mg	65	10
5	210 g	40 mg	188 g	39.8 mg	50	17

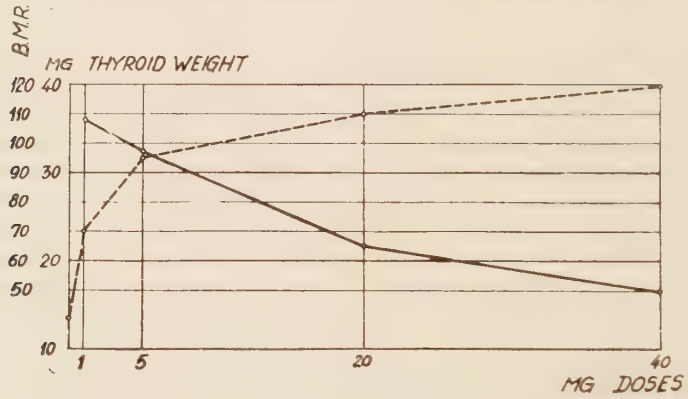


Fig. 19. Curve for the metabolism (o———o) and thyroid weight (o - - - - o) in female rats, 6 months old, treated with methylthio-uracil for 15 days.

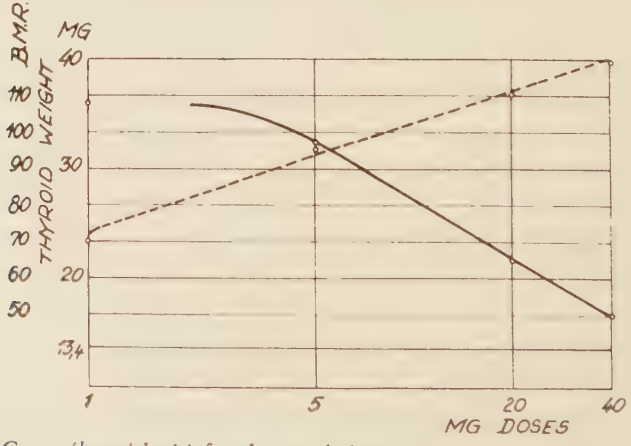


Fig. 20. Curve (*logarithmic*) for the metabolism (o———o) and thyroid weight (o - - - - o) in female rats, 6 months old, treated with methylthio-uracil for 15 days.

The experiments have shown the following features:

a. On treatment of groups of female rats, 6 months old, with methylthio-uracil in daily doses of 5, 20 and 40 mg, respectively for 15 days, the rate of metabolism (from one group to another) falls after a straight line. Under these experimental conditions the rate of metabolism is a logarithmic function of the size of the dose.

b. Under the same experimental conditions as under a, the thyroid weight increases after a straight line. Under these experimental conditions also the thyroid weight is a logarithmic function of the size of the dose (cf. p. 56).

2. *Metabolism and Duration of Treatment (Methylthio-uracil).*

Dose employed: 5 mg methylthio-uracil daily.

Periods of treatment employed: 3, 6, 10, 15, 20, 24, 29, 34, 39 and 42 days.

In this experiment the same animals (10 rats) were used for all

TABLE 20.

Metabolism Determinations on Female Rats, 6 Months Old, under Treatment with 5 mg Methylthio-uracil Daily.

Rat No.	Dates for Determination of Metabolism. 15/2 (3' day)	19/2 (6')	23/2 (10')	28/2 (15')	5/3 (20')	9/3 (24')	14/3 (29')	19/3 (34')	24/3 (39')	27/3 (42')
1220	124	119	121	95	—	—	—	—	—	—
1221	107	115	88	105	71	97	74	55	80	70
1222	118	111	113	104	83	62	68	79	75	73
1223	—	102	—	80	89	98	87	73	81	82
1224	113	114	112	—	97	64	73	73	73	70
1225	121	120	91	93	94	91	75	69	72	67
1226	108	116	100	129	93	95	77	75	88	77
1227	113	114	90	61	90	85	68	79	67	65
1228	111	135	107	88	106	63	76	72	70	71
1229	118	—	113	79	83	74	77	75	91	74
Average metabolism	114	112	104	93	90	81	87	72	77	72

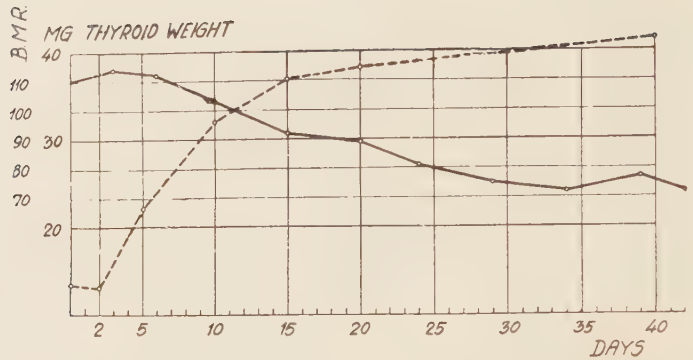


Fig. 21. Curve for the metabolism (o———o) and thyroid weight (o - - - - o) in female rats, 6 months old, treated with 5 mg methylthio-uracil daily.

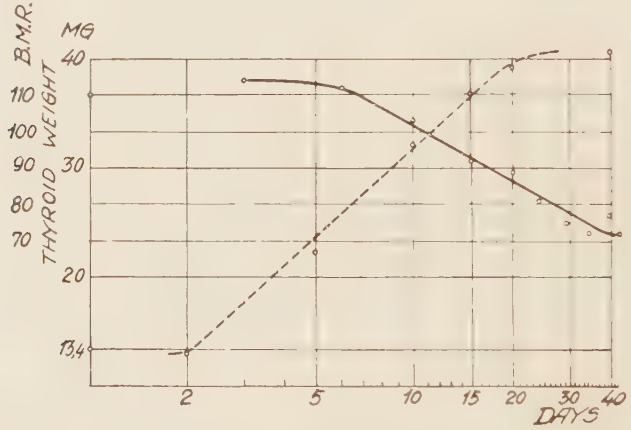


Fig. 22. Curve (*logarithmic*) for the metabolism (o———o) and thyroid weight (o - - - - o) in female rats, 6 months old, treated with 5 mg methylthio-uracil daily.

the metabolism determinations after treatment for the number of days given above. Naturally, then, the thyroid weight of the animal cannot be recorded for comparison. Therefore the thyroid weights from Figs. 6 and 7 are entered for comparison (uniform experimental conditions). One of the rats (No. 1220) died under the experiments from a technical mishap in the introduction of the tube; all the other animals appeared quite unaffected.

These experiments show:

When female rats of 6 months are treated with 5 mg methylthio-uracil daily, the rate of metabolism falls from the 5' to the 40' day of treatment after a straight line. Within this total period and under this treatment the metabolism is a logarithmic function of the duration of treatment.

3. *Metabolism after Discontinuance of Treatment with Methylthio-uracil.*

The following procedure was adopted:

10 female rats of 6 months were treated with 5 mg methylthiouracil daily for 15 days. Then the metabolism of the animals was determined respectively 2, 7, 12, 22, 42 and 83 days after discontinuance of the treatment.

The thyroid weights from Fig. 16 are entered in Fig. 23 for the sake of comparison (uniform experimental conditions).

TABLE 21.

Metabolism Determinations on Female Rats, 6 Months Old, after Treatment with 5 mg Methylthio-uracil Daily for 15 Days.

Treatment with Methylthio-uracil given from 14/2 to 28/2.
Dates for Determination of Metabolism.

Rat No.	2/3 (2' day)	7/3 (7')	12/3 (12')	22/3 (22')	11/4 (42')	22/5 (83' day)
1236	71	95	103	80	62	68
1237	76	88	114	124	109	—
1238	82	64	92	113	—	61
1239	82	66	87	83	—	—
1240	68	75	87	97	62	66
1241	76	89	66	77	67	64
1242	81	90	90	—	106	76
1243	91	95	—	82	92	87
1244	103	103	62	72	—	50
1245	69	67	69	72	64	63
Average metabolism	80	82	85	90	80	66

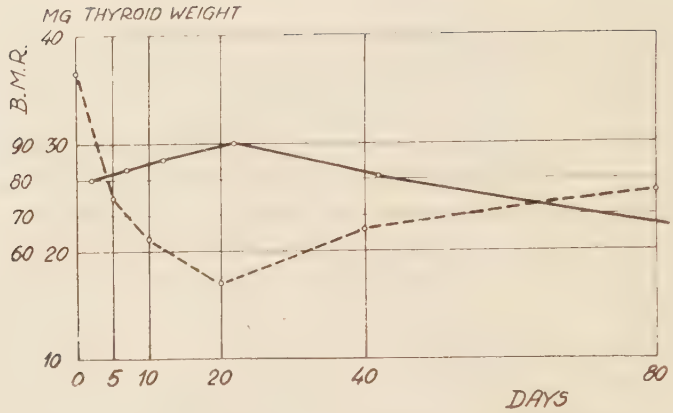


Fig. 23. Curve for the metabolism (o———o)and thyroid weight (o - - - - o) in female rats, 6 months old, *after* treatment with 5 mg methylthio-uracil for 15 days.

Table 21 and Fig. 23 show that in female rats of 6 months treated with 5 mg methylthio-uracil daily for 15 days, the rate of the metabolism two days after the discontinuance of the treatment is about 80. As was to be expected, the rate of metabolism now commences to increase as the antithyroid factor is eliminated from the organism. This increase in the metabolic rate is quite in keeping with the fall in the thyroid weight (see Fig. 23).

After a few weeks, however, there is a secondary fall in metabolism accompanied by a corresponding rise in the thyroid weight. 80 days after the treatment the average thyroid weight was 25 mg. In keeping with this, the average thyroid weight for the rats employed in this experiment was 22 mg on the 84' day after the cessation of the treatment. This rise cannot be attributed to the circumstance that now the animals have become 80 days older. Female rats of 6 months are practically full-grown, on which account a rise in the thyroid weight amounting to 60—70 % within 80 days is improbable. The improbability of this is further accentuated by the fact that not only has the average body weight of the animals failed to increase under the treatment, but it has even decreased — even as long as 80 days after the discontinuance of treatment — although the animals appeared quite unaffected by the treatment (cf. Table 15).

So there seems to be a certain relation between the secondary fall in the metabolism and the secondary rise in the thyroid weight. This is further corroborated by the histological features of the thyroid under the same conditions. As mentioned in the preceding chapter, the histological signs of activity subside after cessation of the treatment; after 20 and 40 days, the histological picture differs but little from that encountered in the controls, even though there are some signs of activity, with marginal vacuolization of the colloid, and here and there a considerable height of the epithelial cells. These changes are more pronounced after 80 days, however, when the histological picture in some of the animals shows merely a slight activity, whereas other animals show rather considerable signs of activity — changes that never are observed in the controls.

To offer an adequate explanation of these findings seems not practicable. Possibly the fall in the rate of metabolism might be attributable to a state of exhaustion of the pituitary, resulting in a diminished production of thyrotropic hormone, as a reaction of the hyperactivity of the pituitary in the hypothyroid state of the animal. But the changes in thyroid go decidedly against such an interpretation. It seems more obvious to assume that these conditions are due to variations in the hormone production of the thyroid due to the action of thio-uracil. But it is not possible to say anything about the details in such a mechanism.

Discussion.

In the literature only rather scanty reports have been made concerning the behavior of the metabolism in animals treated with antithyroid substances.

Mackenzie & Mackenzie[119] found a fall of 10 % in the rate of metabolism in rats of 200 g after treatment for 5—7 days with 2 % sulfaguanidine in the diet. After 10—14 days the fall amounted to 20 %, and it kept at this level to the conclusion of the experiment, on the 40' day. According to *Reineke et al.*[160], 1 % thio-uracil in the diet gives in 14 days in rats a fall in the rate of the metabolism amounting to 23.7 %. *Christensen*[33] states that a daily dose of methylthio-uracil or thio-urea in the course of 1 month reduces the metabolism about 35 % in female rats weighing

200 g. He emphasizes that this effect on the metabolism is roughly proportional to the rise in the thyroid weight. Further, it is to be mentioned that *Reineke et al.*[160] have shown that in rats treated with thio-uracil it requires the same dose of thyroxin to raise the metabolism and lower the thyroid weight to normal values.

Table 20 and Fig. 21 show that 5 mg methylthio-uracil reduces the metabolism in female rats of 6 months on an average by about 33 % after 40 days' treatment. At the same time there is a very marked rise in the thyroid weight, and the histological picture of the thyroid shows evidence of maximal activity. If the inhibitory effect of methylthio-uracil on the formation of the thyroid hormone is complete, the resulting fall in the metabolism will correspond to the fall in metabolism resulting from total thyroidectomy — provided that no thyroxin is produced elsewhere in the organism.

For further elucidation of this question, thyroidectomy has been performed on a number of female rats, 6 months old, weighing about 200 g. As to the procedure in the performance of total thyroidectomy, see Chapter II.

After this, the rate of metabolism was determined on thyroidectomized rats, with employment of exactly the same procedure as in the previous metabolism determinations.

The result of this experiment is recorded in Table 22.

TABLE 22.

Metabolism Determinations on Female Rats, 6 Months Old, after Thyroidectomy (see the text).

Rat No	Number of days after total thyroidectomy																
	8	9	15	18	23	24	30	31	37	45	46	57	63	72	78	112	332
1374	95			66		84		85	76	80			76		68	74	
1375	89			60		73		88		68							
1377	79			80		87		87	79	83			80		85	78	89
1379		101	73		87		77				83	79		65		93	80
1380		72	77		75		70				74	69		64		75	
1381			61		82		70		89		82	71		75		85	83
1382		61	72		70		89		74		77	49		80		95	79
1383		91	70		82		67		68		69	77		58			
Average metabolism	87	81	70	69	79	81	74	86	77	77	77	69	78	68	76	83	82

From Table 22 it is evident that, about 40 days after the operation, the metabolism in the thyroidectomized animals has been lowered on an average by 30 % — which corresponds fairly closely to the fall in the metabolism observed in the same kind of animals on treatment with methylthio-uracil for about 40 days. If from this it be justified to conclude that, under the given experimental conditions, methylthio-uracil has blocked the hormone production of the thyroid completely and thus lowered the metabolism to the level of thyroidectomy, it is essential to ascertain that the organism contains no more thyroid hormone. If this be the case, it seems reasonable to conclude that no more thyroid tissue is present in the organism and that consequently the thyroidectomy has been total.

If remnants of thyroid tissue still are present in the organism after the thyroidectomy, they will undergo a compensatory hypertrophy, and it is to be expected then that the metabolism in such animals will rise again. This did not take place in any of my thyroidectomized animals (see Table 22).

About 60 days after the thyroidectomy all the rats (Table 22) were given 20 mg methylthio-uracil daily through an esophageal tube for 15 days. This very large dose was not able, however, to cause any change in the metabolism of these animals. In Table 22 the "boxed" values give the rate of metabolism after the conclusion of the methylthio-uracil treatment mentioned.

From the experiments here reported, then, it seems rather probable that the administration of 5 mg methylthio-uracil daily for about 40 days is able completely to block the thyroid hormone production. This is in keeping with the findings reported by *Mackenzie & Mackenzie*[119]: that protracted treatment with 2 % sulfaguanidine in the diet produces a fall in the metabolism to the thyroidectomy level, and that administration of sulfaguanidine does not further lower the metabolism in thyroidectomized rats. *Christensen*[33] arrived at the same result, ascertaining by means of histological examinations (serial sections) that the thyroidectomy was total — a procedure which hardly offers greater reliability than the one here employed.

The findings here reported indicate very strongly that physiologically active thyroid hormone is not produced in the organism elsewhere than in the thyroid.

In this chapter it has been shown that in female rats of 6 months the conclusion of treatment with 5 mg methylthio-uracil daily for 15 days subsequently is followed by a rise in the metabolism, which again is followed by a secondary fall. Under the same experimental conditions the thyroid weight shows first a decrease, then a secondary rise. In contrast to these results, *Christensen*[33] states that after discontinuance of the treatment the metabolism soon rises to normal values. *Mackenzie & Mackenzie*[121] treated 2 rats with sulfaguanidine for 52 days, at which point of time the metabolism on an average had fallen to -21 %. After the treatment had been discontinued for 6, 24 and 37 days, the corresponding rates of metabolism were -22, -17 and -22. These authors state that 50 days later there was no evidence of histological activity of the thyroid, but a slight enlargement (no weight given).

As a result of the investigations reported in Chapters V and VI it is further to be emphasized:

Under the following experimental conditions —

a) treatment with increasing doses of thio-uracil or methylthio-uracil daily for 15 days, and
b) treatment with a constant dose of thio-uracil or methylthio-uracil daily for an increasing number of days,

female rats of 6 months shows a fairly high degree of consistency in the effect of the treatment on the thyroid weight, the histological picture of the thyroid and the rate of metabolism.

Chapter VII

EFFECT OF THIO-URACIL ON THE ORGANISM

Purpose of the Present Studies.

In the preceding two chapters an account has been given of the thio-uracil effect on the thyroid and the metabolism in normal rats under varying experimental conditions. Furthermore, the investigations reported in Chapters III and IV indicate that thio-uracil and, in particular, methylthio-uracil will find considerable clinical employment in the treatment of thyrotoxicosis. Therefore it seemed desirable to see whether these substances are able in other fields of the organism to produce unfavorable and undesired changes, which possibly may go against the therapeutic employment of the substances.

The studies that will be reported in the following are to be looked upon in connection with the laboratory examinations performed on patients who have been treated with thio-uracil and methylthio-uracil (see Part II, Chapter IV).

When the present investigations were commenced, a few reports had been made in the literature on observations showing that especially thio-urea, though also thio-uracil, in some patients gave rise to serious changes in the blood picture (leukopenia and thrombopenia). Therefore these investigations were aimed in particular at the effect of the thio-uracil therapy on the hematopoietic organs and on the peripheral blood in patients and in experimental animals. In addition, histological examination has been made of the liver and kidneys from animals given relatively large amounts of thio-uracil. Furthermore, on the patients determinations were made of serum cholesterol and blood urea under continued treat-

ment with thio-uracil; besides, the urine was examined regularly for albumin. Finally these investigations were undertaken also for the purpose of revealing any possible effect on some of the other endocrine glands, and to ascertain the general condition and weight of the animals in the course of the treatment.

The procedure adopted in these experiments has been mentioned already in Chapters II and V, on which account the details will not be mentioned here.

The experiments were carried out on rats exclusively.

The investigations were performed after 3 different methods of treatment:

a. Female rats of 6 months were treated with a single, medium-size, daily dose for 40 days, given through an esophageal tube:
   Thio-uracil: 10 mg daily for 40 days.
   Methylthio-uracil: 5 mg daily for 40 days.
b. Female rats of 6 months were treated with a single large dose daily for 15 days, through an esophageal tube:
   Thio-uracil and Methylthio-uracil: 80 mg daily for 15 days.
c. Female and male rats, 12 days old, treated with subcutaneous injection of thio-uracil 3 times a week for 7 months (see p. 72).

The thio-uracil effect on the thyroids under these experimental conditions is reported in Chapter V.

1. *The Thio-uracil Effect on the General Condition and Weight of the Animal:*

a. Moderate dose given for 40 days (thio-uracil 10 mg daily, methylthio-uracil 5 mg daily): Apparently the animals were quite unaffected by the treatment, thriving normally, gaining in weight. Objective examination shows no particular effect.
b. Large daily dose for 15 days (thio-uracil and methylthio-uracil 80 mg daily): The animals were affected but quite slightly, being less lively than normally; the animals treated with methyl-thio-uracil were losing considerable weight (see Table 23). Otherwise no particular abnormality observed.

TABLE 23.

Female Rats, 6 Months Old, Treated with Thio-uracil and Methylthio-uracil through Esophageal Tube. (see Tables 9, 10, 11, 12).

Number of rats	Initial weight	Dosage	Weight after treatment	μ
7	205 g	10 mg thio-uracil daily for 40 days	212 g	8
6	203 g	5 mg methylthio-uracil daily for 40 days	216 g	12
5	213 g	80 mg thio-uracil daily for 15 days	208 g	10
6	211 g	80 mg methylthio-uracil daily for 15 days	192 g	17

c. Female and male rats were treated from the 12' to the 205' day of life with subcutaneous injections of thio-uracil (as to dosage, see p. 72). During this continuous treatment the animals were a little less lively than normally, but otherwise the objective examination revealed no particular abnormality.

The animals were thriving normally. The fur developed normally in the young and remained normal throughout the treatment. The effect of the treatment on the thyroid is mentioned on p. 73.

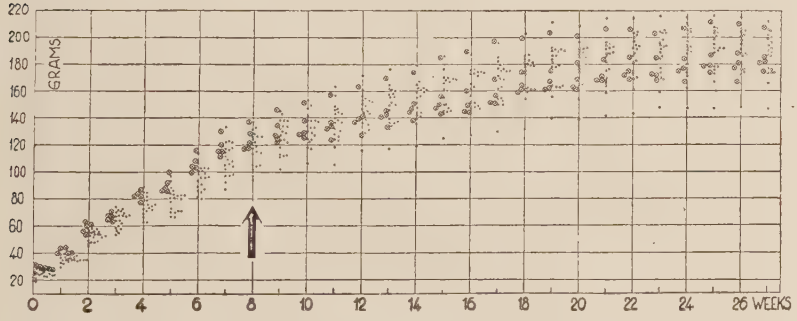


Fig. 24. Body weight of 25 female rats, 20 of which were treated with thio-uracil from the 12' to 205' day of life. o: experimental animals. ⊕: controls. ↑: indicates the point of time when the young were removed from the mother. The average body weight of additional 25 untreated female rats born at the same date was 195 g (27 weeks old).

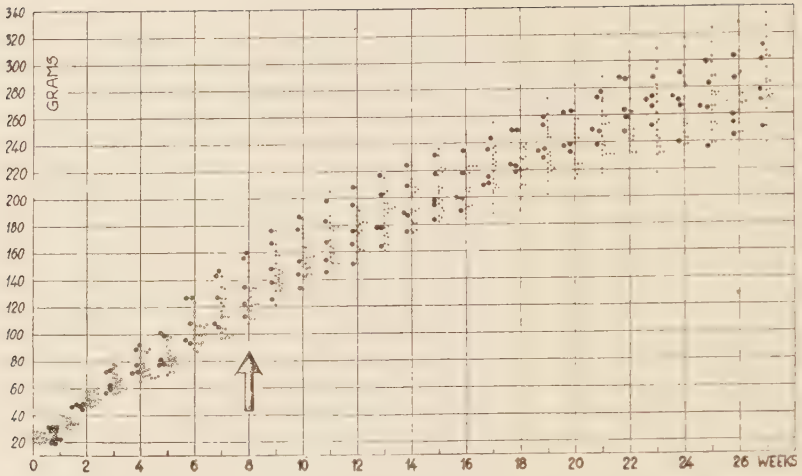


Fig. 25. Body weight of 25 male rats, 20 of which were treated with thio-uracil from the 12' to the 205' day of life. o: experimental animals. ⊕: controls. ↑: indicates the point of time when the young were removed from the mother.

The effect on the body weight is evident from Figs. 24 and 25 in which it is compared with the weight of the controls.

Discussion.

Williams, Weinglass et al.[206] state that thio-uracil has a growth-inhibiting effect on the treated animals, and that this inhibition is distinct as early as after 10 days of treatment, involving the weight of the animal as well as the growth, and also the size of all the organs except the thyroids. This inhibition, the authors state, appears to be brought about by the effect of thio-uracil on the formation of thyroid hormone. In addition, thio-uracil inhibits the effect of the growth-hormone injected at the same time. *McGavack et al.*[118] arrived at the same result. The same applies to *Astwood*[15] who states that the changes observed (decrease in growth, development and food intake) are in concordance with the state of hypothyroidism.

In contrast hereto, *Mackenzie & Mackenzie*[121] found that 2 % sulfaguanidine was tolerated well by rats, and that the growth during this treatment was normal. *Freiesleben et al.*[53] found no particular change in rats that were treated for periods not

exceeding 8 months with a daily dose of 10—20 mg methylthio-uracil per 100 g rats; nor did this treatment produce any change in the fur of the animals. Under the treatment the animals were somewhat sluggish, but they presented no other toxic symptoms. Nor did *Christensen*[33] find any toxic effect from large doses of methylthio-uracil given through a considerable length of time.

In the experiments here reported a decisive inhibition of the growth of the animals was seen only after treatment with 80 mg methylthio-uracil daily. This dose must be considered very large and undoubtably the inhibition of growth has been due to a toxic effect on the animals.

In some experiments no decrease in growth was seen during constant thio-uracil treatment for about 7 months. The given dose has to be considered slight, it is true, but nevertheless at the conclusion of the experiment the thyroid weight showed an increase of about 400 % as compared to that of the controls (cf. Table 17).

Thus the experiments have shown that the slight but unquestionable thio-uracil effect on the organism does not inhibit the development in growing rats. It seems very likely, however, that thio-uracil which to a higher degree inhibits the synthesis of the thyroid hormone in this way may cause some inhibition of growth. These observations may be of importance in the treatment of pregnant thyrotoxicosis patients with thio-uracil.

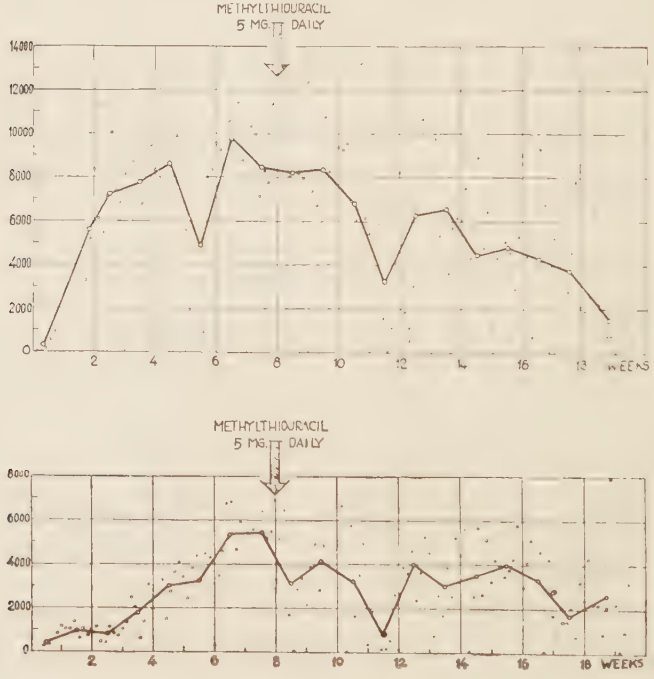
2. *Thio-uracil Effect on Muscular Activity.*

It has been mentioned above that rats under treatment with thio-uracil and methylthio-uracil in large doses (80 mg daily) or with thio-uracil in smaller doses but through a long period are less lively than normal rats of the same age. It is not surprising, however, that thio-uracil treatment has this effect on the animals. A hypothyroid state of the organism develops under this treatment, and it is reasonable to expect, among other things, that this condition will bring about a reduction in the muscular activity.

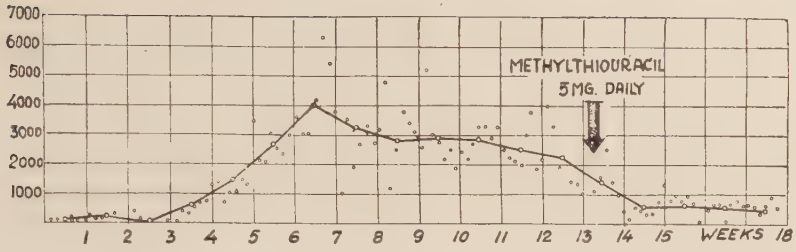
An attempt has been made through the tread-mill experiments mentioned below to get some impression of the influence of thio-uracil treatment upon the muscular activity in normal rats. These experiments were carried out on 2 female rats of 6 months,

weighing 200 g (I and II), and 2 male rats of the same age (III and IV). The animals were placed in ordinary wire cages with access to a tread-mill made up of bicycle wheels (without tires), between the frames of which a wire screen, about 20 cm wide, was stretched for the rat to run on. Prior to the treatment with methylthio-uracil the animals stayed in the cage with appertaining tread-mill for 2—3 months in order to get accustomed to these conditions, and the number of rotations of the wheel was recorded every day. Then the rats were given 5 mg methylthio-uracil daily — in the usual manner, by means of an esophageal tube, in 1 ml water. All the animals stood the introduction of the tube without any inconvenience. Rat III died after treatment for about 1 month, however, owing to a technical mishap during the employment of the tube; the animal aspired the fluid and died immediately.

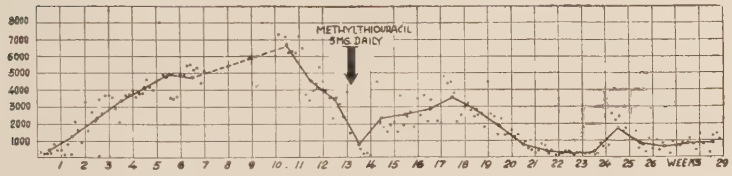
The results of these experiments are evident from Fig. 26. The



II



III



IV

Fig. 26. I. Female rat. II. Female rat. III. Male rat. IV. Male rat. Curves for the muscular activity (tread-mill experiments) in rats before and during treatment with methylthio-uracil (see the text).
↓ indicates the point of time for the commencement of the treatment.

number of revolutions for each day is indicated by dots. The circles through which the curves are drawn give the average numbers of revolutions per week.

As mentioned, the animals stood this treatment well, presenting no symptoms referable to the introduction of the esophageal tube, apart from the accident to rat III. In particular, it is to be noted that the animals presented no pulmonary symptoms.

The two female rats (I and II) weighed the same at the conclusion of the experiment as at its commencement (200 g). The initial weight of rats III and IV was 200 g, and during the three months in which the animals were not given methylthio-uracil, their weight increased respectively to 325 and 345 g. At the conclusion of the experiment, rat IV had lost 20 g (weight 325 g).

At the end of the experiment rats I, II and IV were sluggish and somewhat dull; their gait was unsteady, and the animals put the entire ball of their foot (hind legs) to the ground. The fur was quite normal. Roentgenography of their bones (lower extremities) showed normal conditions. Autopsy revealed no abnormality besides a large goiter.

While these experiments gave no convincing results, they still seem to have shown a distinct tendency to a fall in energy and muscular activity in the animals during protracted treatment with a medium dose of methylthio-uracil. The dose employed has a quite considerable effect on the thyroid (cf. Chapter V) and on the metabolism (cf. Chapter VI), and the decreasing energy and muscular activity of these animals is quite in keeping with the hypothyroid state developing in the animals as a result of the treatment.

3. *Thio-uracil Effect on the Bone Marrow, Spleen and White Blood Count, besides on the Liver and the Kidneys.*

I. *Bone Marrow, Spleen, Liver and Kidneys.*
Experimental Conditions:

A. Moderate dose given for 40 days.
Thio-uracil: 10 mg for 40 days: 5 rats.
Methylthio-uracil: 5 mg for 40 days: 6 rats.

B. Large dose for 15 days.
Thio-uracil: 80 mg for 15 days: 5 rats.
Methylthio-uracil: 80 mg for 15 days: 6 rats.

All 24 rats (females, 6 months old) were killed with gas 24 hours after the last dose. The bone marrow of the femur was removed, smeared on slides, fixed with methyl alcohol, and stained with acid eosin-methylene blue (Grübler's solution); also the spleen, liver and kidneys were removed, and preparations were made for histological examinations — as described in Chapter II.

Examinations of the bone marrow were obligingly performed by Dr. *A. Søeborg Ohlsen,* who has thoroughly examined all the smears, making differential counts on 7 of them, the first four of which came from animals treated with 5 mg methylthio-uracil daily for 40 days (Nos. 500, 501, 502 and 504), the last three from rats given 10 mg thio-uracil daily for 40 days (536, 537 and 538). In each differential count, 400 cells were counted.

The outcome of these differential counts it recorded in Table 24.

On going through all the bone marrow smears (24 rats) a fairly close concordance of the histological features could be demonstrated. Pathological changes were not observed in any of the animals.

TABLE 24.

Differential Counts on Bone Marrow in Rats Treated with Methylthio-uracil or Thio-uracil daily for 40 Days.

(Se the text.)

	Female rats No.				Male rats No.		
	Female 500	Female 501	Female 502	Female 504	Male 536	Male 537	Male 538
Myeloblasts	4.50%	1.25%	4.25%	1.00%	1.75%	4.00%	4.25%
Promyelocytes	1.25	0.50	3.25	0.25	0.75	0.75	1.00
Neutrophil myelocytes	4.75	15.50	14.00	6.50	4.25	6.75	6.00
Eosinophil myelocytes	5.00	5.50	0.25	2.25	6.75	6.00	7.00
Basophil myelocytes	0.25	0	0	0	0.25	0	0
Metamyelocytes + rod-shaped neutrophil leucocytes	22.25	29.00	21.00	35.75	26.50	27.75	35.50
Polymorphonuclear neutrophil leucocytes	21.75	31.50	19.00	18.25	14.25	16.00	8.00
Eosinophil leucocytes	5.50	1.00	0.25	0.50	0.75	0	2.75
Basophil leucocytes	0	0	0	0	0	0	0
Lymphocytes	32.50	15.25	35 25	34.75	43.00	37.00	35.00
Monocytes	0	0	0	0	0	0	0
Plasma cells	1.75	0.50	1.50	0.75	0.75	1.25	0.25
Megakaryocytes	0.25	0	1.00	0	1.00	0.25	0.25
Reticulum cells	0.25	0	0	0	0	0.25	0
Per 400 cells of "the white system" were found:							
Erythrogonia	10	3	2	3	4	0	3
Erythroblasts, basophil	32	15	59	40	63	49	62
Erythroblasts, eosinophil	17	12	47	38	33	22	34

Histological examination of the spleen, liver and kidneys from all 24 rats revealed no difinite pathological changes.

II. *White Blood Cells.*

Experimental Conditions.

C. Female and male rats treated with subcutaneous injections of thio-uracil from the 12' to 216' day of life (dose as given on p. 72).

Altogether 20 female and 20 male rats were treated. 5 female and 5 male rats (controls), born on the same day, were kept under exactly the same experimental conditions except for the thio-uracil treatment. At the end of the treatment, blood was taken from the artery of the tail for white blood count and differential count (usual technique).

Results: the outcome of the *white blood counts* is recorded in Table 25.

TABLE 25.

White Blood Counts in Female and Male Rats treated with Thio-uracil from 12' to 216' Day of Life (see the text), and in the Controls.

		Average of white blood count	μ
Experimental animals	20 female rats Nos. 705—724	15.180	3000
	20 male rats Nos. 730—749	13.425	3000
Controls	5 female rats Nos. 725—729	16.360	5000
	5 male rats Nos. 750—754	14.440	5000

Differential count: The results are given in Table 26.

TABLE 26.

Differential Counts of White Blood Corpuscles in Female and Male Rats Treated with Thio-uracil from 12' to 216' day of Life (see the text), and in Controls.

			Leukocytes			
		Lympho-cytes	Polynu-clear	Rod-shaped	Eosino-phil	Mono-cytes
Experimental animals	20 female rats Nos. 705—724	71.7	21.6	2.7	0.5	3.3
	20 male rats Nos. 730—749	72.1	25.2	1.3	0.2	1.1
Controls	5 female rats Nos. 725—729	79.6	12.4	4.6	0.4	3.0
	5 male rats Nos. 750—754	66.0	32.4	1.2	0	0.4

From Tables 25 and 26 it will be noticed that neither the total number of white blood cells nor the numbers of the individual forms of white blood cells deviate from the values found for the controls. In the various experimental groups the individual values come close to the average values given.

Discussion.

Under the above-mentioned experimental conditions the thio-uracil effect in rats has not given rise to pathological changes in the cell content of the bone marrow nor in the white blood count.

Under thio-uracil treatment, according to *Williams*[201], a relatively marked concentration of the substance is found in the bone marrow. Further, *Williams & Bissell*[203] state that the greater part of the thio-uracil content of the blood is found in the cells of the blood — with its highest concentration in the white blood cells.

As a matter of fact, an estimation of the influence of the thio-uracil treatment on the bone marrow and blood picture in animals has been mentioned only by a few authors. *Williams, Weinglass et al.*[206] found no pathological changes in nearly 50 rats which were treated with thio-uracil for 7—90 days. On the other hand, in a few of these animals the authors found low values for the number of white blood cells (in heart's blood). The authors state that the hemoglobin percentage was inclined to be rather low, whereas the icterus index was normal. The authors emphasize that the thio-uracil concentration in the blood of the animals generally was higher than the concentration found in man. Here it is to be mentioned, however, that in man the thio-uracil concentration in the bone marrow is also relatively high (*Palmer*[152]).

Christensen[33] found no toxic effect on rats from large doses of thio-urea and methylthio-uracil given through a long period. *Freiesleben et al.*[53] state that treatment with fairly large doses of methylthio-uracil for up to 8 months produced no toxic symptoms in rats, nor histological changes in the muscles, liver, kidneys, gonads, parathyroids or adrenals of these animals. *Williams, Weinglass, Bissell & Peters*[206] treated 25 rats with 1/4 % thio-uracil in the drinking water for 7—60 days, and — in keeping

with the above — they found no pathological changes in the skeleton musculature, heart, lungs, thymus, pancreas, spleen, liver, kidneys, intestines, lymph glands, brain or spinal cord, nor in the weight and histological features of the adrenals. Further, they had given 0.6 g thio-uracil daily for 6—28 days to patients who all were suffering from a fatal lesion outside the thyroid. Postmortal examination of the brain, lungs, spleen, liver, kidneys, adrenals, pancreas, gonads, thyroid, and bone marrow, besides — in 4 of the cases — of the brain and pituitary, showed no structural changes that might be attributed to the thio-uracil treatment.

Mackenzie & Mackenzie[121] state that in an experiment where some rats were treated with 3 % sulfaguanidine in their diet, one-half of the animals showed concretions in the urinary system; and in patients under thio-uracil treatment *Palmer*[152] has observed crystaluria and microscopic hematuria. A few times, the writer has noticed that the urine from rats treated with thio-uracil or methylthio-uracil was intensely red in colour. The urine was not collected; and even though it was suggestive of hematuria, no proof of this has been obtained.

4. *Thio-uracil Effect on the Pituitary.*
   Experimental Conditions.
   A. Moderate doses of thio-uracil or methylthio-uracil daily for 40 days.
   B. Large doses of thio-uracil and methylthio-uracil daily for 15 days.
   (For dosage, see Table 27.)

The experiments were carried out exclusively on female rats, 6 months old. 24 hours after the last dose, the animals were killed, and, among other organs, the pituitary was removed, weighed and prepared for histological examination (as described in Chapter II). The size of the dose and the weight of the pituitary after the treatment are recorded in Table 27. For the sake of comparison, it is to be mentioned that the average weight of the pituitary in *10 controls* (female rats of the same age and weight) was found to be 8.8 mg (μ: 1.9).

From Table 27 it will be noticed that the average pituitary weight in all four experimental groups was a little higher than the

TABLE 27.

Female Rats, 6 Months Old, Treated with Thio-uracil and Methylthio-uracil.

Number of rats	Initial weight	Dosage	Weight after treatment	Pituitary weight	μ
7	205 g	10 mg thio-uracil daily for 40 days	212 g	10.0 mg	0.8
6	203 g	5 mg methylthio-uracil daily for 40 days	216 g	9.2 mg	2.3
5	213 g	80 mg thio-uracil daily for 15 days	208 g	11.2 mg	1.3
6	211 g	80 mg methylthio-uracil daily for 15 days	192 g	9.1 mg	1.3

average for the controls. But, it may hardly be decided whether this difference has been due to the treatment.

The histological examination of the pituitary in the same 24 rats showed normal cellular structures without any sign of degeneration.

Discussion.

Under the above-mentioned experimental conditions no definite changes in the pituitary were seen that could be ascribed to the treatment with thio-uracil and methylthio-uracil.

Nor did *Williams, Weinglass et al.*[206] find any pathological changes in the pituitary of rats even after 60 days of treatment with thio-uracil. These authors further state that in relation to the body weight the pituitary remained normal. On the other hand, *Mackenzie & Mackenzie*[119, 121] were able to demonstrate some changes in the anterior pituitary lobe in rats treated with sulfaguanidine, stating that as early as after 2 weeks of treatment there was a demonstrable degranulation and loss of acidophil cells, besides vacuolization and increase in the number and size of basophil cells — corresponding to the findings after thyroidectomy. The authors emphasize that the occurrence of these findings without degeneration of the gonads presumably is a result of thyroid hypofunction. *Griesbach*[63] found similar changes in rats treated with rape seeds, which contain a derivative of thio-urea. On treatment

of the rats through a considerable length of time, *Mackenzie & Mackenzie*[119] found an almost complete absence of acidophil cells in the anterior pituitary together with an increase in the so-called thyroidectomy cells, whereas *Griesbach*[63] under continued treatment found an increase in acidophil cells, while the thyroid at the same time commenced again to produce colloid. He emphasizes that apparently there is a marked parallelism between the cellular changes in the pituitary and the stimulation of the thyroid; when the thyroid hyperplasia is at its height, the basophil cells in the anterior pituitary predominate and are in a secretory phase.

5. *Thio-uracil Effect on the Ovaries and Uterus together with the Estrous Cycle in Rats.*

As mentioned in the preceding section, the thio-uracil effect appears to induce a state of increased activity of the anterior pituitary. Presumably this is attributable to a lowered inhibition of the pituitary, resulting from the inhibitory effect of thio-uracil on the production of the thyroid hormone, which, in turn, results in a shift in the state of balance between the two glands. This question will be dealt with more thoroughly in Chapter IX, in which it also is shown that presence of the pituitary is a *conditio sine qua non* for the development of goiter in rats under thio-uracil treatment. It seems justified to assume that this goiter formation is brought about by an increased output of thyrotropic hormone even though it cannot be excluded that the thyroid at the same time becomes more sensitive to the action of this hormone.

The experiments that will be mentioned in the following were carried out partly to look for possible histological changes in the ovaries induced by a direct thio-uracil effect on these organs, partly to decide whether, besides the increased production of thyrotropin, the state of increased activity of the pituitary under thio-uracil treatment might also give rise to a considerable increase in the gonadotropin production. For, if this be the case we may expect to find the ovaries enlarged — owing to the formation of corpora lutea — as well as an increased output of folliculin which again will influence the uterine weight and estrous cycle of the animal.

In Chapter V some experiments were reported in which female rats of 6 months were treated with increasing doses of thio-uracil and methylthio-uracil (from 1/4 to 80 mg daily) for 15 days and respectively with 10 mg thio-uracil and 5 mg methylthio-uracil daily for an increasing number of days (from 2 to 40 days). In several of these animals the ovaries and uterus were removed too, the animals being killed 24 hours after administration of the last dose. These organs were cleaned and weighed, and the ovaries were prepared for histological examination as described in Chapter II.

The ovarian and uterine weights after treatment with thio-uracil and methylthio-uracil are recorded in Tables 28 and 29 and in Figs. 28—30. For comparison, it may be mentioned that the ovarian and uterine weights in 10 untreated female rats of the same weight and age were found to be as follows:

Ovarian weight, average: 78.0 mg (μ: 16.6).
Uterine weight, average: 441 mg (μ: 147).

TABLE 28.

Ovarian and Uterine Weight in Female Rats, 6 Months Old, Treated with Thio- or Methylthio-uracil for 15 Days.

Number of rats	Initial weight	Daily dose	Weight after treatment	Ovarian weight	μ	Uterine weight	μ
		Thio-uracil					
5	204 g	1 mg	211 g	69.3 mg	13	531 mg	200
5	201 g	2½ mg	208 g	71.3 mg	7	556 mg	250
5	222 g	5 mg	223 g	63.4 mg	11	406 mg	80
5	231 g	10 mg	230 g	59.0 mg	11	438 mg	150
5	209 g	20 mg	218 g	78.0 mg	13	312 mg	70
5	204 g	40 mg	202 g	62.0 mg	14	440 mg	50
5	213 g	80 mg	208 g	72.3 mg	9.5	366 mg	110
		Methylthio-uracil					
5	202 g	1 mg	211 g	61.8 mg	8		
5	209 g	2½ mg	210 g	73.4 mg	4.9	450 mg	75
5	225 g	5 mg	226 g	77.0 mg	6.0	367 mg	90
5	202 g	10 mg	219 g	69.6 mg	8.0		
5	201 g	20 mg	201 g	73.5 mg	8.5	369 mg	190
6	199 g	40 mg	198 g	69.7 mg	19	332 mg	95
6	211 g	80 mg	192 g	50.5 mg	16	256 mg	110

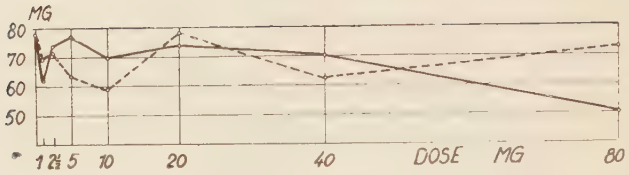


Fig. 27. Curves for the ovarian weight in female rats of 6 months, treated with thio-uracil (o - - - - o) or methylthio-uracil (o——o) for 15 days.

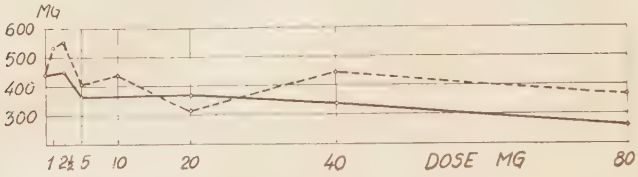


Fig. 28. Curves for the uterine weight in female rats of 6 months, treated with thio-uracil (o - - - - o) or methylthio-uracil (o——o) for 15 days.

TABLE 29.

Ovarian and Uterine Weight in Female Rats, 6 Months Old, Treated with 10 mg Thio- or 5 mg Methylthio-uracil Daily.

Number of rats	Initial weight	Duration of treatment	Weight after treatment	Ovarian weight	μ	Uterine weight	μ
		10 mg thio-uracil daily					
5	203 g	2 days	205 g	64.1 mg	14		
5	231 g	15 days	230 g	59.0 mg	11	438 mg	150
5	202 g	20 days	213 g	62.8 mg	8	557 mg	95
7	205 g	40 days	212 g	59.1 mg	13	482 mg	170
		5 mg methylthio-uracil daily					
5	200 g	2 days	198 g	68.9 mg	8.5		
5	226 g	5 days	227 g	75.0 mg	14	435 mg	140
5	225 g	15 days	226 g	77.0 mg	6	367 mg	85
5	201 g	20 days	214 g	65.8 mg	14	467 mg	120
6	203 g	40 days	216 g	77.2 mg	22	444 mg	173

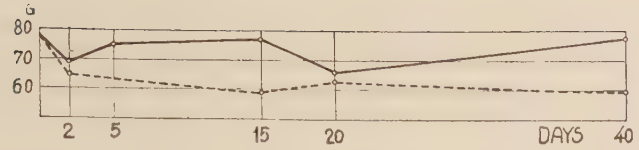


Fig. 29. Curves for ovarian weight in female rats, 6 months old, treated with 10 mg thio-uracil (o - - - - o) or 5 mg methylthio-uracil (o———o) daily.

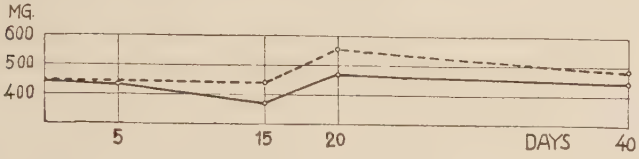


Fig. 30. Curves for the uterine weight in female rats, 6 months old, treated with 10 mg thio-uracil (o - - - - o) or 5 mg methylthio-uracil (o———o) daily.

N.B.! The uterus was always empty of fluid when it was weighed. As no scrapings were taken from the vaginal mucosa at the same time the phase of the estrous cycle of the respective animals cannot be given.

From Tables 28 and 29 and from Figs. 27—30, it will be noticed that under the given experimental conditions the ovarian and uterine weights for the animals did not undergo any particular changes under the treatment with thio-uracil or methylthio-uracil.

Histological examination was made of all the ovaries removed, and it revealed no changes that might indicate that the ovaries had been exposed to an increased luteinizing influence from the anterior pituitary, nor any changes ascribable to a direct effect of thio-uracil or methylthio-uracil.

The thio-uracil effect on the estrous cycle in rats was likewise examined.

Technique: From 8 female rats of 6 months, weighing about 200 g, vaginal smears were made daily for 3 weeks; scrapings from the vagina were spread on a slide, fixed, and stained with methylene blue. All the smears showing 100 % cornified cells are designated as positive, the others as negative. Cornification of all the cells in the smears is evidence of the estrous stage proper, which in rats appears at intervals of about 5 days.

After this, the rats were treated with 10 mg thio-uracil daily (given through esophageal tube as a suspension in 1 ml water with addition of 5 % mucilage) for 4 weeks, while, at the same time, vaginal smears were made daily and estimated as described above.

Thirty days after the commencement of the thio-uracil treatment the animals were killed, and the thyroid, ovaries and uterus were removed and weighed as described in Chapter II, with the following results:

Average thyroid weight: 35.6 mg μ: 5.5
Average ovarian weight: 62.8 mg μ: 16
Average uterine weight: 419 mg μ: 105

The estimations of the vaginal smears have not been included in this text. No deviations from the normal state were found.

So, under the given experimental conditions, the thio-uracil treatment has had no definite influence on the estrous cycle of the treated animals.

Discussion.

On treatment of female rats of 6 months with thio-uracil or methylthio-uracil under varying experimental conditions (*e. g.*, large daily doses (80 mg) for 15 days and moderate doses (5—10 mg) daily for up to 40 days) no variations were observed in the ovarian and uterine weights for the treated animals, and the histological picture of the ovaries or in the estrous cycle of the animals that might be ascribed with certainty to a direct or indirect (via the anterior pituitary) effect of thio-uracil or methylthio-uracil.

Williams, Weinglass, Bissell & Peters[206] have looked into the testicular and ovarian weights for rats treated with thio-uracil, and they found the weight in these animals to be lower than in untreated rats, while the ratio between the respective organ weight and the body weight of the animals remained normal. Nor were any histological changes seen. By injection of pregnancy urine and chorionic gonadotropin together with thio-uracil into young female rats, these authors were able to show that administration of thio-

uracil does not alter the formation of follicles and corpora lutea in these animals. Further, *Mackenzie & Mackenzie*[121] have examined the behavior of the estrous cycle in 4 young female rats after treatment with 2 % sulfaguanidine given with the food for 4 weeks, and they too found no changes in the estrous cycle under this treatment.

6. *Thio-uracil Effect on Serum Calcium and Serum Phosphate in Rats.*

The following experiments were carried out, among other reasons, because thyrotoxicotic patients treated with thio-uracil and methylthio-uracil sometimes give low values for serum calcium without showing any clinical signs of hypocalcemia (cf. Part II, Chapter IV).

Technique.

Altogether 20 female and 20 male rats were treated with subcutaneous injection of thio-uracil from the 12' to 216' day of life (for dosage, see p. 72), while 5 female and male rats (controls), born on the same day, were kept under exactly the same experimental conditions — except for the thio-uracil treatment.

The treated animals as well as the controls were born on 10/8/44, and the treatment was commenced on 22/8.

On 28/2/45 and 15/3 — *i. e.*, after respectively 191 and 216 days of thio-uracil treatment — blood was taken from the caudal artery in the animals for determination of serum calcium and serum phosphorus. Prior to the withdrawal of the blood, the animal had been fasting for 24 hours.

The calcium and phosphorus analyses were obligingly carried out by *Bodil Schmidt-Nielsen,* dentist, the calcium analyses after a method worked out by *Schmidt-Nielsen* herself[171a]. The method employed for the phosphorus analyses, which has been described by *Kjerulf-Jensen*[97a], is a modification of *Lohmenn & Jendrassik's* method, which again is a modification of the original method given by *Brigg.* In a private communication, concerning her modification of the method, *Schmidt-Nielsen* states: "The accuracy of the individual calcium analysis, for the amount here analyzed,

is about 1.5 %. On the other hand, the accuracy of the phosphate analyses is only about 5 % when the amounts analyzed are as small as here."

The analytical results are recorded in Table 30.

From Table 30 it will be noticed that there is a marked concordance between the values for serum calcium as well as for serum phosphorus obtained in the individual rats within the same experimental group. Furthermore, there are no particular deviations between the values for the treated animals and for the controls.

In addition, in all 50 rats the *bones of the lower extremities*

TABLE 30.

Serum Calcium and Serum Phosphorus Values obtained in Female and Male Rats after 191—216 Days' Thio-uracil Treatment.

Experimental Animals					Experimental Animals			
Female rat No.	Serum Calcium		Serum phosphorus		Male rat No.	Serum calcium	Serum phosphorus	
	mg%	mg%	mg%	mg%		mg%	mg%	mg%
705	10.1	9.6	9.0	4.8	730	9.1	8.1	7.1
706	9.7	—	9.8	—	731	9.2	9.6	7.4
707	10.0	9.5	10.3	4.8	732	9.1	9.1	7.2
708	9.0	9.6	8.1	6.8	733	9.4	7.4	7.7
709	8.9	8.4	8.6	6.5	734	9.5	7.5	6.9
710	9.3	9.9	6.4	5.5	735	9.4	8.7	6.8
711	9.1	9.3	8.0	7.4	736	9.1	8.9	7.6
712	9.6	9.8	6.6	5.4	737	9.6	7.5	6.4
713	8.4	8.9	8.3	6.0	738	9.8	5.7	6.6
714	8.2	8.6	6.9	5.5	739	9.9	7.1	7.6
715	8.6	9.6	7.0	5.6	740	9.2	6.9	8.2
716	8.9	—	7.3	—	741	9.3	5.6	6.9
717	8.9	9.9	7.8	6.9	742	10.0	6.4	6.4
718	9.2	10.0	6.3	6.2	743	9.7	4.4	8.4
719	8.8	9.4	6.2	5.5	744	9.4	6.0	6.8
720	9.2	9.2	6.1	7.4	745	9.8	6.1	7.1
721	9.8	9.9	7.8	6.0	746	9.9	5.8	7.4
722	9.7	9.9	7.1	7.5	747	10.3	5.9	7.7
723	8.7	9.3	5.9	7.4	748	10.0	6.3	7.7
724	9.8	9.9	6.6	8.6	749	10.2	5.0	7.2
Average results	9.2	9.5	7.5	6.3		9.6	6.9	7.3

Controls					Controls			
Female rat No.	Serum Calcium		Serum phosphorus		Male rat No.	Serum calcium	Serum phosphorus	
	mg%	mg%	mg%	mg%		mg%	mg%	mg%
725	9.5	9.9	6.4	6.5	750	9.9	6.1	7.2
726	9.7	10.0	7.0	6.9	751	10.1	4.6	6.4
727	9.3	9.3	7.6	5.3	752	9.6	4.4	5.1
728	9.8	9.9	6.4	6.0	753	9.7	5.3	8.9
729	9.7	10.0	7.3	6.3	754	9.9	6.1	6.1
Average results	9.6	9.8	6.9	6.2		9.8	5.3	6.7

were examined roentgenographically, and in all the animals this examination showed perfectly normal conditions. In particular it has not been possible roentgenologically to demonstrate any decrease in the calcium content of the bone in the treated animals as compared to the controls.

From the findings reported above it seems justified to conclude that under the experimental conditions here adopted the thiouracil treatment has caused no essential change in the calcium and phosphorus content of the organism of the animals, and hence it is not likely to have had any injurious effect on the parathyroids of the animal.

Chapter VIII

FATE OF THIO-URACIL IN THE ORGANISM

Absorption.

Under otherwise uniform experimental conditions, the subcutaneous administration of thio-uracil to female rats of 6 months has a greater effect on the thyroid weight than when given by mouth.

TABLE 31.

Female Rats, 6 Months Old, Treated with Methylthio-uracil (MT) and Thio-uracil (T) for 15 Days.

Number of rats	Initial weight	Dosage	Weight after treatment	Thyroid weight	μ
11	206 g	MT.: 2.5 mg daily perorally	208 g	33.1 mg	8.3
12	202 g	MT.: 2 mg daily subcutaneously	215 g	36.4 mg	3.1
5	208 g	T.: 10 mg every other day perorally	215 g	20.0 mg	3.0
6	216 g	T.: 10 mg every other day subcutaneously	218 g	26.7 mg	3.6

The experiments recorded in Table 31 indicate that the absorption of the drug is greater on subcutaneous injection than from the intestinal canal, possibly because a larger amount of the substance is destroyed in the intestinal canal than in the subcutis. Even on autopsy after protracted experiments the author has never noticed any unabsorbed substance in the subcutaneous tissue. The absorption of this substance from the peritoneal cavity is likewise complete.

Williams[201] states that thio-uracil given by mouth is absorbed from the digestive tract, the substance being non-demonstrable in the feces. The absorption proceeds rapidly (*Williams*[201], *Williams & Bissell*[203], *Palmer*[152]); and more than 80 % of it disappears from the digestive canal within the first two hours (*Williams*[201]). It is difficult to say whether thio-uracil is destroyed in the digestive canal. *Williams*[201] states, however, that the excretion of the substance with the urine is about 15 % greater after intravenous injection than after oral administration, and he ascribes this difference to destruction in the digestive tract.

Thio-uracil in the Blood.

After oral administration, thio-uracil can soon be demonstrated in the blood. In rats the concentration of the substance after a single dose becomes maximal after 30 min. (*Williams*[201]). In man, *Palmer*[152] found the blood concentration of thio-uracil to be at its maximum after 15 min. *Williams & Bissell*[203] arrived at the same result after administration of a single dose of 0.2 g. *Mackenzie & Mackenzie*[121] found that the sulfaguanidine concentration in the blood of rats roughly is proportional to the percental content of this substance in the food.

In the blood the greater part of the thio-uracil is found in the cells (*Williams & Bissell*[203]); the concentration is greatest in the white blood cells (*Williams & Bissel*[203], *Palmer*[152]), but the total amount is greater in the red blood cells.

Thio-uracil disappears rapidly from the blood and also from the organism. On intravenous injection of 5 mg thio-uracil, *Williams*[201] was able one minute later to demonstrate 94 % of the substance in the organism; and this figure indicates also the accuracy of the method. After 1 hour he found 65 % of the injected substance; after 3 hours, 30 %; after 10 hours, 22 %; and after 24 hours, merely a trace. But even though the substance soon appears to leave the blood stream, a remnant of it may still be demonstrated here for a long time. Thus, after a single dose of thio-uracil, *Palmer*[152] was able to demonstrate this substance in the blood for up to 3 days. After discontinuance of thio-uracil administration to patients, *Williams*[201] was able to demonstrate the

presence of this substance in the blood for up to 3 days when the daily dose had been 0.6 g or less, while with a larger daily dose the presence of the substance in the blood could be demonstrated for up to 5 days.

Under thio-uracil treatment the concentration of this substance in the blood is highly labile. On an average, it is considerably higher when a certain amount of thio-uracil is given in several portions during the day than when the same amount is given in a single dose (*Williams*[201]). This is in keeping with the observation that the destruction of the substance in the organism increases with its increasing concentration in the blood.

Distribution in the Rest of the Organism.

In order to look into the distribution of thio-uracil in the various tissues and fluids of the organism (rats), the writer commenced some experiments with radio-active "marked" methylthio-uracil, but, through a regrettable accident, all the preparations from these animals were thrown away. A new experiment on a single rat gave no measurable difference. Owing to war-time restrictions of the supply of electricity, new amounts of the radio-active methylthio-uracil could not be obtained, and these experiments had to be given up.

Other authors have shown, however, that thio-uracil is distributed throughout the organism, being demonstrable in practically all the tissues and fluids of the organism. Still, the distribution of this substance throughout the organism is not uniform. Thus, *Williams*[201] states that the highest concentration of the substance is found in the pituitary, thyroid, adrenals, bone marrow and milk. *Palmer*[152] states that in man the highest concentration of the substance is found in the pituitary, adrenals and bone marrow.

Williams, Bissell, Jandorf & Peters[204] gave 1 g thio-uracil daily to patients suffering from some fatal disease. Determination of the thio-uracil content of various organs post mortem showed a higher concentration in the adrenals than in most other tissues. In pregnant rats, given thio-uracil during the last two weeks of pregnancy, this substance could be demonstrated in the placenta in a concentration which, expressed by the dry-weight percentage,

appeared to be rather higher than in the maternal organism. The presence of the substance could be demonstrated in the young ones too, but here it amounted to only about one-half of that found in the mother. The young ones weighed about 20 % less than the controls, and they presented a goiter with considerable hyperplasia of the thyroid. Also *Williams*[201] states that thio-uracil is able to pass through the placenta. Furthermore, *Eaton*[42], who treated two pregnant women with thio-uracil, mentions that one child was born with an enlarged, though soft, thyroid, the contours of which could be made out on the neck of the child. Otherwise the child appeared to be well; there were no respiratory difficulties, and the child thrived normally. Three months after its birth, the goiter had disappeared, and the weight of the child was normal. Also *Palmer*[152], who likewise has treated pregnant women with thio-uracil, states that the child 5 months after delivery was perfectly normal. Finally, it is to be mentioned that, according to *Williams, Weinglass et al.*[206] thio-uracil given to female rats in sufficient amount may be excreted with the milk and produce a distinct goiter in the young.

The non-uniform distribution of the substance in the organism seems to be of considerable importance to the understanding of its effect on the organism as well as the untoward effect.

On comparison with urea, according to Marshall & Davis[131], a rather uniform distribution is here found in all the tissues of the organism, both when the substance is present in normal and in abnormally high concentration. The concentration is a little lower in adipose tissue, and a little higher in the urinary system, but otherwise it corresponds practically to the urea concentration of the blood.

Excretion.

On intravenous injection of a solution of urea, this substance will soon be excreted with the urine (*Marshall & Davis*[131]) and the same applies to thio-urea. Thus, on oral administration *Lange*[107] (1892) was able to demonstrate this substance in the urine within 3 hours.

After administration of 1 g thio-urea by mouth, *Campbell*,

Landgrebe & Morgan[28] were able to demonstrate this substance in the urine as early as within 1 hour. After 10 hours, 75 % of the substance was excreted; after 24 hours, 96 %. Also thio-urea appears to be distributed in all the tissues of the organism.

Thio-uracil, too, appears to be removed from the organism fairly rapidly. When present in the organism the substance will exert its inhibitory effect on the synthesis of thyroid hormone. The correctness of this view is plainly evident from the experiments reported in Chapter V and VI. When this substance is removed from the organism this will soon be noticeable from the thyroid weight, which thus may be used as a criterion in the rough estimation of the rate at which thio-uracil is removed from the organism.

TABLE 32.

Female Rats, 6 Months Old, Treated with Thio-uracil and Methylthio-uracil for 15 Days
(see Tables 13 and 14).

Number of rats	Initial weight	Dosage	Weight after treatment	Thyroid weight	μ
		Thio-uracil			
7	205 g	3.33 mg three times daily	200 g	32.6 mg	3.1
11	218 g	10 mg daily	220 g	27.4 mg	3.6
5	208 g	10 mg every other day	215 g	20.0 mg	3.0
5	209 g	10 mg every third day	214 g	17.7 mg	1.9
		Methylthio-uracil			
7	207 g	1.67 mg three times daily	204 g	37.9 mg	6.6
11	214 g	5 mg daily	217 g	36.8 mg	8.5
10	217 g	5 mg every other day	219 g	21.9 mg	5.0
5	227 g	5 mg every third day	235 g	17.4 mg	2.9

From Table 32 it is evident that the effect on the thyroid weight, especially in treatment with thio-uracil, is increased noticeably when a certain amount of the substance is distributed over several doses in the course of the day than when it is given as a single dose. Furthermore, this effect subsides markedly when the same total dose is given every other or every third day.

This can only mean that the thio-uracil concentration in the thyroid decreases rapidly; and it seems justified therefore to

conclude that something similar applies to the concentration of this substance in the blood. This rapid fall in the thio-uracil concentration of the blood must be due either to conversion (destruction) of the substance or excretion from the organism.

Thio-uracil is excreted with the urine in unchanged form. After institution of thio-uracil treatment, *Anderson*[10] found at first only a slight amount of thio-uracil in the urine. As the treatment was continued, however, the excretion reached a level of 60—70 %. *Williams*[201] states that a considerable part of a dose of thio-uracil given to a human subject may be demonstrated in the urine within the first 2 hours. If this dose is given by mouth, no excretion can be demonstrated within the first 30 min. On the other hand, if the dose is given intravenously, there is a noticeable excretion even within this period. When given by mouth, the substance is found to be fully excreted within 24 hours, whereas on intravenous injection its complete excretion takes 48 hours. Possibly, this difference may be due to a more firm combination between thio-uracil and the red blood cells when the substance is given intravenously.

When thio-uracil is given by mouth in a dose of 0.2 g every 4 hours it takes about 24 hours for the thio-uracil concentration of the blood and its excretion with the urine to become constant (*Williams & Bissell*[203]). If this dosage is maintained for several days, the thio-uracil concentration of the blood will be 3 mg%, and the urinary output 300 mg per day. The daily excretion is only 35 % of the dose taken daily, and thus it deviates considerably from the values found by *Anderson*[10]. In this connection, however, it is to be mentioned that the percental output of the substance with the urine decreases with the increasing total dose. *Williams, Kay & Jandorf*[205] state that one-third of the thio-uracil given is excreted with the urine. After administration of a single dose of methyl-thio-uracil *Mørch*[144] found an excretion of the substance amounting to 45—50 % within 48 hours, meaning an excretion of about 40 % during the first 24 hours, the remnant during the next day, and nothing during the third day. If thio-uracil treatment (0.6 g or less as a daily dose) be discontinued, generally no thio-uracil may be demonstrated in the urine after 3 days[201].

Destruction in the Organism.

As mentioned already, the output of thio-uracil in the urine is about 15 % greater when the dose is given intravenously than on oral administration. *Williams*[201] thinks that this difference is due to destruction of the substance in the digestive canal. The amount of thio-uracil destroyed in the digestive canal should be equal to the amount of thio-uracil excreted within the first 30 min. when the substance is given intravenously. *Williams*[201] thinks that, apart from this, the destruction of thio-uracil in the organism is the same after intravenous administration as after oral.

According to *Williams*[201], as mentioned, 3 hours after intravenous injection of 5 mg thio-uracil it has been possible to demonstrate only 30 % of the substance in the organism. During the same period a considerable amount of the substance was excreted with the urine, but no numerical value is available for this excretion. Still, the excretion appears to be far from 70 %; and thus a part of the substance has either been destroyed or converted in the organism. *Williams*[201] claims that the higher the thio-uracil concentration in the blood the more rapidly does its destruction take place.

That the destruction of thio-uracil appears to take place in the organism is evident from the fact that administration of thio-uracil gives an increased excretion of neutral sulphur, which may be explained as due to the administration of the sulphur-containing thio-uracil (*Williams*[201]). At the same time the excretion of inorganic sulphur is lowered, and generally this applies also to the excretion of "etheral" sulphur. On severe damage to the kidney, only very little thio-uracil is excreted with the urine (*Williams, Kay & Jandorf*[205]) and yet the blood concentration of the substance is not altered. So the authors found it conceivable that the liver might decompose thio-uracil; still, they did not find the thio-uracil concentration of the blood to be greater in patients with advanced sclerosis of the liver than in normal subjects.

Fresh specimens of tissue, removed from many organs, proved capable of thio-uracil decomposition. According to the individual weight of these organs the pituitary appeared to be the most active in this respect, followed by the thyroid and the adrenals. Muscular and pancreatic tissue were found to be the least active (*Williams, Kay & Jandorf*[205]).

Chapter IX

INTERACTION OF THE ENDOCRINE SYSTEM

The interaction of the endocrine glands is the problem which still has been solved only in part. A knowledge of this interaction as far as practicable, however, is essential in order to understand the changes taking place in the thyroid under treatment with thio-uracil. A very comprehensive literature on this question has been published already, and it would take us too far here to go into its details. The purpose of this chapter is merely to pick out a few questions concerning the interaction between the thyroid, pituitary and ovaries that may appear to play some rôle in connection with the action of thio-uracil. It is to be emphasized at once, however, that numerous factors, still unknown, make it impossible clearly to survey this question.

In the endocrine system, the pituitary occupies a central position. Sometimes it has been designated as "the master gland" or the "keystone of the endocrine arch". *Jores*[91] states that the anterior pituitary lobe has as its task exclusively to adjust and regulate the mutual activity of the peripheral glands; he further claims that the total correlation of the endocrine system takes place through the hormones of the anterior pituitary lobe — of which hormones at least 10 have been recognized. Even though more close investigations into the problems will reduce the number of these hormones, it still seems most likely that their number will be so large that we will have to assume several pituitary hormones to be produced by each of the two hormone-producing types of cells (acidophil and basophil), establishing a sort of parallelism between the production of these hormones. Indeed, investigations reported by *Franck*[48] point in this direction; and *Jores*[91] has

emphasized that clinically we have learned this to be the case. Among other things, he cites that we do not know of any pituitary lesion that may be associated with a faulty production of a single hormone, and that it always involves a disturbance in the production of a group of hormones.

The thyroid-stimulating pituitary hormone was recognized in 1929 by *Schwartzbach & Uhlenhudt*[172]. In 1931, *Aron*[11], who also is to be mentioned in this connection, distinguished between a thyroid- and an ovarian-stimulating hormone. Furthermore, the presence of pituitary thyrotropic hormone in the blood and its stimulating effect on the thyroid has been reported by *Caulaert, Aron & Stahl*[30], *Krogh, Lindberg & Okkels*[102], *Loeb & Bassett*[109], *Loeser*[111, 112], *Okkels*[150], *Rowland & Parkes*[166] etc. Also the influence of the hormone on the metabolism by way of the thyroid is mentioned. In this way *Friedgood*[54] produced experimentally a thyrotoxicosis-like condition in guinea-pigs; and *Krogh, Lindberg & Okkels*[102] were further able to show that this hormone produces hypertrophy of the Golgi apparatus of the thyroid cells. *Marine & Rosen*[130] were able to produce exopthalmus by means of the same hormone.

The stimulating effect of the thyrotropic hormone on the histological features of the thyroid and its physiological activity has been established. But, the thyroid hormone appears to inhibit the output of thyrotropic hormone. Thus *Loeser*[111] and *Adams & Jensen*[5] have been able experimentally to show that the thyrotropic hormone content of the anterior pituitary in mice is lowered when the animals are treated with thyroxin. Something similar was demonstrated to apply to rats by *Hohlweg & Junkmann*[80] and by *Kuschinsky*[106]. Further, *Reforzo — Membrives* (cited after Ann. Review of Biochem. 13, 1944, p. 430) demonstrated that the anterior lobe of the pituitary from rats that have been treated with dried thyroid substance, lowers the thyroid weight of the guinea-pig and decreases the height of the epithelial cells in the thyroid, just as the metabolic rate of the guinea-pig falls considerably.

If, on the other hand, the amount of thyroid hormone in the organism is lowered, there will be an increase in the output of thyrotropic hormone (*Marine & Rosen*[130]). In concordance here-

with, *Houssay et al.*[82] found that thyroidectomy produces hypertrophy of the pituitary. Further, *Loeser*[111] shows that the thyrotropic hormonal content of the blood increases when the thyroid is removed. The same has been demonstrated by *Emerson & Cutting*[43], who — like *Rawson & Starr*[157] — also found an increase in the thyrotropic content of the blood in thyroidectomized patients.

The strumogenic factors in the diet mentioned in *Chapter I* will likewise bring about a decrease in the amount of thyroid hormone, causing a compensatory increase in thyrotropic hormone. Fundamentally it is the same factors that produce goiter in rats treated with thio-uracil. The observations here presented demonstrate quite plainly the interaction between the thyrotropic hormone and the thyroid hormone.

Aron & Benoit[14] emphasize that the relation between the gonadotropic factors of the anterior pituitary and ovarian folliculin is quite analogous to the relation between the thyrotropic hormone and the thyroid hormone. Like *Hohlweg*[79], the authors emphasize that estrin is able to inhibit the elimination of the ovary-stimulating anterior pituitary hormone. This has further been demonstrated by *Zondek*[210] and, in parabiotic experiments, by *Cuterly & Cuterly*[35]. Further the same has been demonstrated clinically in women by *Frank & Salmon*[49]. *De Amilibia et al.*[8] report, however, that in rats the treatment with estrin for 5 days has a quite considerable stimulating effect on the histological features in the thyroid; but, the authors are unable to say whether this effect takes place via the pituitary.

Mazer & Israel[133] discussed this question very thoroughly stating that large doses of estrin within a short period have a stimulating effect on the function of the anterior pituitary, whereas protracted administration of estrin in doses larger than indicated physiologically gives rise to secondary regressive changes in the function and structure of the ovary through inhibition by the anterior pituitary. These authors state that if estrin is given for several months it is able entirely to abolish certain of the functions of the anterior pituitary. In this connection it is to be mentioned that *Franck*[48], *Hohlweg*[79], *Wolfe & Chadwick*[208] and

Wolfe & Wright[209] have shown that treatment with estrin is able to alter the histological features of the anterior pituitary in a quite considerable degree.

In contrast hereto, lowered or abolished estrin effect in the organism gives rise to an increased output of gonadotropic hormone. In castration experiments, for example, *Houssay, Novelli & Sammartino*[82], *Kippen & Loeb*[98] *and Nielson*[147] have established this fact. Here it is to be mentioned that changes in the anterior pituitary lobe after castration, according to *Hohlweg & Junkmann*[80], do not correspond to the changes found after thyroidectomy.

The interaction between two endocrine glands has been mentioned above. The disturbance of the equilibrium between such glands, however, will, as might be expected, also give rise to other disturbances in the endocrine system.

Thus *Aron & Benoit*[14] show that protracted employment of estrin is able not only to inhibit the output of gonadotropic hormone but also to inhibit the output of thyrotropic hormone (together with the growth hormone and the lactogenic and diabetogenic hormone). It is emphasized, however, that in guinea-pigs the administration of estrin produces no changes in the appearance of the thyroid. *Grumbrecht & Loeser*[66] were able with estrin to produce a transitory decrease in the activity in the thyroid of the rat with a decrease in the activity in the functional yield of the thyroid; and *Karp & Kostkiewicz*[93] were able with large doses of folliculin to produce goiter in rabbits. *Mazer, Israel & Alpers*[134] found no structural changes in the thyroid after large doses of estrin given within a short period; but they state that protracted administration of estrin lowers the histological activity of he thyroid. According to *Kunde, d'Amour et al.*,[105] subcutaneous injection of estrin made no difference in the metabolism in normal dogs.

On the other hand, *Aron & Benoit*[14], as well as *Grumbrecht & Loeser*[66] have shown experimentally that when estrin is given simultaneously or prior to thyrotropic hormone it may be able to inhibit the stimulating effect of this hormone upon the thyroid.

As has also been the writer's experience with guinea-pigs, these

observations are difficult to explain, as both hormones are injected in their finished state. It seems most reasonable to assume that the injected amount of estrin inhibits the normal production of thyrotropic hormone in the anterior pituitary of the animal, even though this does not exclude a direct effect on the thyroid of the animal. *Aron & Benoit*[14] are rather in favour of the third possibility: that estrin somehow neutralizes the finished thyrotropic hormone or exerts an antagonistic effect on the organs.

The fact that estrin apparently is able to inhibit the thyrotropic hormone production of the anterior lobe of the pituitary is evident from the experiment mentioned below, in which the estrin-treated rats are also given methylthio-uracil. From experiments reported before, we know that methylthio-uracil in the dose here employed gives a considerable goiter in the animal. Here the changes in the thyroid are taken roughly as a measure of the increased output of thyrotropic hormone by the pituitary. Control experiments show that estrin by itself alone has no decisive effect on the nature of the thyroid or on its histological features, on which account a direct effect of estrin on the thyroid may hardly be of any importance.

Experiments have been carried out with estradiol benzoate as well as synthetical estrin (sexadien Leo) in doses that have to be looked upon as very large. All the experimental animals have been female and male rats, 6 months old. Besides the experiments mentioned here, the author has performed a number of similar experiments, among others, with thio-uracil too; the results, however, are quite like those reported here. The given dose was always administered as a single daily dose. Methylthio-uracil was given through an esophageal tube, suspended in 1 ml water with addition of 5 % mucilage. On the other hand, estradiol benzoate and sexadien were given subcutaneously under the skin of the back dissolved in 0.25 ml oil. 24 hours after the last dose was given, the animals were weighed, and killed by gas. Then the thyroid and pituitary were removed and prepared for histological examination (as described in Chapter II). The procedure adopted for the histological examination has been mentioned on p. 34. Also the ovaries and uterus were removed from several of the animals, but their

histological examination presented no changes of particular interest. The histological changes in the pituitary after estrin treatment are not to be mentioned here in particular.

TABLE 33.

Experiments with Estradiol Benzoate and Synthetic Estrin (Sexadien Leo) as well as with Methylthio-uracil.

Nos. of rats	Sex	Initial weight	Treatment	Weight after treatment	Thyroid weight	μ	Pituitary weight	μ	Histological activity of the thyroid
10	Female	205 g	None		13.4 mg	1.9	8.8 mg	1.9	0
10	Male	210 g	(Controls)		10.3 mg	1.7	5.5 mg	0.8	(+)
11	Female	214 g	Methylthio-uracil	215 g	36.8 mg	8.5			+++
5	Male	224 g	5 mg for 15 days	243 g	34.8 mg	8.4			+++
5	Female	208 g	Estradiol benzoate	203 g	12.7 mg	2.1	22.6 mg	3.6	0
6	Male	203 g	5000 I. B. U. for 25 days	199 g	9.8 mg	3.3			(+)
6	Female	205 g	Sexadien	192 g	12.9 mg	2.9	21.8 mg	8.5	0
6	Male	213 g	1/2 mg for 25 days	198 g	11.9 mg	2.1	19.0 mg	5.5	(+)
7	Female	209 g	Estradiol benzoate 5000 I. B. U. for 25 days +	190 g	22.1 mg	3.8	24.8 mg	6.0	− −
5	Male	210 g	Methylthio-uracil 5 mg for the last 15 days of the period	184 g	20.8 mg	4.7	24.3 mg	5.0	++
5	Female	201 g	Sexadien 1/2 mg for 25 days +	186 g	21.3 mg	5.5	25.3 mg	2.9	++
5	Male	209 g	Methylthio-uracil 5 mg for the last 15 days of the period	192 g	24.1 mg	4.3	25.0 mg	7.5	++

These experiments show that, under the given experimental conditions, estradiol benzoate as well as synthetic estrin (Sexadien Leo) in rats are able to inhibit, but not to prevent, the strumogenic effect of methylthio-uracil in a very pronounced degree. Correspondingly, the histological picture of the thyroid shows a less pronounced activity, but this histological activity is decidedly

stronger than would have been expected from the weight of the thyroid. On this account the estrin appears to inhibit the formation of new follicles more than it can reduce the increase in histological activity.

In this respect the effect of estradiol benzoate and sexadien is about the same. Presumably this effect is due to the inhibitory action of the two substances mentioned on the anterior pituitary lobe, which therefore produces a smaller amount of thyrotropic hormone. A priori, however, we cannot exclude a direct effect of these substances upon the thyroid; but, if such an effect exists it may be looked upon as non-essential.

Here, it is further to be mentioned that the writer has performed hemithyroidectomy on a fairly large number of female rats 6 months old. At this operation, if there was any recognizable difference in the size of the two lobes (see Chapter II), the larger is removed. After the operation, then, the animals were divided into three groups.

Group I (9 rats): no treatment; killed 16 days after the operation.

Group II (9 rats): 10 days prior to the operation and 15 days after this the animals were treated with estradiol benzoate, 5000 I. B. U. (subcutaneously) daily. The animals were killed 16 days after the operation.

Group III (9 rats): After the operation treated with 5 mg thiouracil daily (through esophageal tube) for 15 days. Killed 16 days after the operation.

After the animals were killed, the remaining lobe of the thyroid was removed, weighed and prepared for histological examination just like the lobe removed at the operation.

Results.

In the animals of Group I a slight compensatory hypertrophy of the remaining thyroid lobe could be demonstrated, as a rule, together with a slight, but not definite increase in its histological activity.

The animals in Group II (treated with estrin) showed no

definitely demonstrable compensatory hypertrophy; nor could any definite difference be demonstrated between the two lobes.

In Group III, as was to be expected, the remaining lobe of the thyroid had undergone a very marked enlargement, with very pronounced signs of histological activity.

For Groups I and II the experiments have been of too short duration, and they give no distinct or convincing results, on which account they just are to be mentioned here.

In keeping with what has been said above, a decrease in the estrin content of the organism not only gives rise to an increased output of gonadotropic hormone but also of thyrotropic hormone (*e. g., Aron & Benoit*[14], *Kippen & Loeb*[98], *Loeser*[113]). However, *Starr & Bruner*[182] have not been able to confirm this finding. *Feuchtinger*[47], *Jores*[91] and *Loeser*[113] emphasize that this fact plays a rôle in the development of the climacteric hyperthyreosis, which may arise when the inhibitory effect of the estrin upon the anterior pituitary subsides as a result of the ovarian insufficiency in the climacteric state.

Feuchtinger[47] further states that the usual enlargement of the thyroid in the beginning of the climacteric is due to the increased output of thyrotropic hormone. He treated patients presenting climacteric hyperthyreosis with estrin and found good results from this treatment.

In two of my own cases — patients suffering from thyrotoxicosis that developed in the climateric state — I have tried treatment with very large doses of estrin (Ovex Leo) through a considerable length of time, but the therapeutic results were by no means convincing. In this connection it is to be mentioned that, in keeping with the theory that estrin suppresses the activity of the basophil cells in the anterior pituitary, *Dunn*[41] has treated 11 patients suffering from Cushing's syndrome (basophil adenoma) and in benign forms of this illness he obtained some surprisingly good therapeutic results, but not in the malignant forms.

Mazoplasia which, according to *Mazer & Israel*[133], is due to disharmony of the pituitary-ovarian mechanism — with overproduction of mamma-stimulating hormone from the anterior pituitary

lobe — has likewise been treated with estrin by these authors, who state that 24 out of their 39 patients were cured in this way.

Further it is to be mentioned that *Czoniczer & Kleiner*[36] in patients suffering from thyrotoxicosis have observed a metabolism-decreasing effect from treatment with anterior pituitary hormone (»glanduantin« and »prehormone«), and that *Starr & Patton*[183, 184] as well as *Falta & Högler*[45] have successfully treated patients suffering from thyrotoxicosis with »antuitrin«, a luteinizing hormone obtained from urine of pregnant women. *Starr & Patton*[184] emphasize, however, that this form of therapy is effective only when the ovarian function is intact; without being able to explain the reason why, they think that the effect of the treatment depends upon a normal ovarian function.

Mazer & Israel[133] say that in the constitutional state designated as Graves' disease, the thyroid manifestations are most likely brought about by a hyperfunction of the anterior pituitary lobe, with excessive production of the thyrotropic hormone. However, no increase in the amount of thyrotropic hormone can be demonstrated in the blood or urine from patients with thyrotroxicosis (*Bodart & Fellinger*[23], *Emerson & Cutting*[43], *Fellinger*[46], *Hertz & Oastler*[74], *Krogh & Okkels*[104], *Rawson & Starr*[157], *Smith & Moore*[177]). On the contrary, the amount of thyrotropic hormone seems rather somewhat reduced.

Through experiments in vitro as well as in vivo, however, *Seidlin*[173] has shown that the thyroid appears to play a quite considerable role in the removal of the thyrotropic hormone from the organism. *Gordon, Goldsmith & Charipper*[61] arrived at the same result. *Rawson, Graham & Riddell*[156a] have been able further to show that in experiments in vitro the thyrotropic hormone is inactivated by pieces of tissue from the thyroid, and that this phenomenon is even more pronounced when the experiment is carried out with pieces of tissue from hyperplastic and hyperactive thyroid, whereas it almost fails to appear when the pieces of tissue come from hypoplastic glands.

As already mentioned, it is practicable experimentally — by means of the thyrotropic hormone — to produce a condition in experimental animals that quite reminds of thyrotoxicosis. There-

fore, it seemed obvious to assume that this hormone would also be present in increased amounts in patients suffering from thyrotoxicosis. If so, the aforementioned observations by *Rawson et al*[156a] might possibly afford an explanation of why it has not been possible to demonstrate the presence of this hormone in such patients. But if thyrotoxicosis is associated with an increased output of this hormone from the anterior pituitary, the ratio between the gonadotropic hormone and the estrin in the organism under the same condition will be of considerable interest. So far, however, we cannot with any degree of certainty form an opinion as to the relative amount of these hormones in the organism because the etiological factors of thyrotoxicosis are still unknown.

In order to throw some light on this question, the writer has performed hormonal analyses on 24-hour urine from 6 patients with severe to moderate thyrotoxicosis.*) These 6 patients comprise 1 man, aged 23, and 5 menstruating women, aged 32—50 years. All hormonal analyses were serial examinations covering 3—4 weeks, in which period all the urine of the respective patients was collected. The institution of the iodine therapy was postponed, so that the hormonal analyses were carried out for about two weeks before any iodine treatment was given and for about two weeks after the institution of iodine therapy. In all 6 cases the output of gonadotropic hormone was estimated as well as that of estrin and testis hormone. While these hormonal analyses are not to be discussed in detail here, it still is to be mentioned that throughout the experimental period none of the patients showed any value deviating from the normal values, and that the iodine treatment did not alter the value in any noticeable degree.

So the possibly increased amount of thyroid hormone in these patients, suffering from thyrotoxicosis appears to have had no influence on the anterior pituitary output of gonadotropic hormone or on the estrin production of the ovaries. In this connection it is to be mentioned that *Horn*[81] has been able experimentally to show

*) I am greatly obliged to Professor E. Meulengracht for his kind permission to perform these studies on patients admitted to Dep. B of the Bispebjerg Hospital. The analyses were carried out in the Biological Laboratory of Løvens kemiske Fabrik, Copenhagen.

that an excessive amount of thyroxin may promote the excretion of estrin — something, which, according to *Mazer & Israel*[133], has been observed clinically too.

Finally it is to be emphasized that female rats which were treated with thio-uracil or methylthio-uracil for up to 40 days (cf. Chapter VII) showed no noticeable changes whatever in the ovarian or uterine weight, nor changes in the histological features of the ovaries even though the treatment had reduced the amount of thyroid hormone in the organism quite considerably.

In conclusion it is to be pointed out that the interaction of the endocrine gland system is not limited to the glands mentioned here — just as the interference of the thio-uracil effect with the equilibrium of the endocrine system may assert itself also in other aspects — *e. g.*, the function of the adrenals. In this connection it may be mentioned that, according to *McGavack et al.*[118], thio-uracil promotes the adrenomegalic effect of the adrenotropic hormone of the anterior pituitary lobe — something that has been observed also by *Kennedy & Purves*[95] in rats, treated with rape seeds, which — as shown by *Kennedy*[94] — contain a derivative of thio-urea. Further *Williams, Bissell, Jandorf & Peters*[204] state that, in some patients, the administration of thio-uracil in daily doses of 1 g led on to retention of sodium chlorine, nitrogen, creatine and creatinine, suggesting a hyperadrenocortical effect.

Chapter X

THE THIO-URACIL EFFECT

The experiments mentioned in the preceding (Chapters V and VI) showed that rats treated with thio-uracil develop goiter and hyperplasia of the thyroid parenchyma. At the same time the metabolism of the animals is decreasing, so that it is reasonable to assume that a state of hypothyroidism has developed in the organism of the animals.

According to *Harington*[70] we do not yet know with certainty the actual nature of the circulating thyroid hormone even though there are many things to indicate that it is the iodine-containing thyroxin. *Harington*[70] has ventilated the possibility that it may be the thyroglobulin, or a peptide derived herefrom that may contain both diiodotyrosine and thyroxin. Nor do we know the mode of action of this hormone. So far it may be said with certainty only to exert a peripheral action on the tissue, and that it has a stimulating effect on the metabolic processes. But no details in these processes are known as yet.

If a state of hypothyroidism develops in the rat treated with thio-uracil, it will be reasonable to assume that the amount of thyroid hormone in the organism of the animal is lowered. *Mackenzie & Mackenzie*[121] think that they are able to exclude the possibility of an increased demand for this hormone in the tissues.

In the literature available to me I have not been able to find anything that proves directly that the amount of circulating thyroid hormone is lowered in animals treated with strumogenic substances. On the other hand, numerous authors have dealt with the effect of these substances on the normal physiological processes

in the thyroid; some of the results obtained in this respect will here be reviewed briefly.

It is well-known that iodine, after its absorption by the thyroid, is synthesized to diiodotyrosine and thyroxin. *Schachner, Franklin & Chaikoff*[170] emphasize that the thyroid possesses a capacity for quick removal of large amounts of circulating iodine from the blood.

According to *Hertz & Roberts*[75] the thyrotropic hormone is able to stimulate the capacity for the concentration of iodine; and in keeping herewith *McGavack et al.*[118] assert that the reaccumulation of iodine after thio-uracil treatment is delayed when the pituitary is removed or when the animal is given thyroxin. In this connection it may by mentioned that *Hertz, Roberts & Salter*[76] have been able to demonstrate an increased "avidity" for iodine in hyperplastic thyroid from patients with Graves' disease.

Furthermore, *Harington*[70] points out that the thyroid, which is the only organ in the organism that contains iodine in noticeable amount, absorbs about 10—15 % of the injected, radio-active ("marked") iodine as soon as within 2 hours; after 48 hours the absorption amounted to 50 %. In the thyroid, this iodine was found both in the form of inorganic iodine, diiodotyrosine and thyroxin, but the concentration was greatest in the diiodotyrosine fraction. The formation of diiodotyrosine appears to proceed rapidly, whereas its further transformation into thyroxin proceeds slowly. According to *Harington*[70], the transformation into thyroxin takes place through oxidizing processes — something that is confirmed through the fact that in laboratory experiments it is possible directly to oxidize diiodotyrosine to thyroxin.

In Chapter I it has been mentioned that absolute or relative iodine deficiency in the organism may give rise to a goiter with hyperplasia of the thyroid parenchyma. We have to assume that the iodine deficiency inhibits the thyroid in producing a sufficient amount of the iodine-containing thyroid hormone, so that the balance between this hormone and the thyrotropic hormone of the anterior pituitary is disturbed, resulting in an overproduction of thyrotropic hormone. In such cases the supply of iodine will be able to reestablish normal conditions.

As the thyroid changes encountered in rats treated with thio-uracil are of the same character as the changes brought about by iodine deficiency, it seems obvious to assume that also the thio-uracil effect on the organism involves an absolute or relative iodine deficiency. *Campbell, Landgrebe & Morgan*[28] found that the thyroid changes produced by thio-urea correspond fairly closely to the thyroid changes due to iodine deficiency, on which account they assumed thio-urea to combine with the iodine and thus inhibit the iodine absorption by the thyroid. For thio-urea has a particular chemical affinity for iodine, together with which it forms formamidin-disulphide-hydro-iodide. A few authors[52, 77] likewise state that administration of iodine has no influence upon the effect of thio-uracil on the thyroid. For further elucidation of this question, the following *experiment* was carried out:

TABLE 34.

Female Rats, 6 Months Old, Treated with Iodine, Diiodotyrosine and Methylthio-uracil for 15 Days.

Number of rats	Initial weight	Daily treatment	Weight after treatment	Thyroid weight	Histological activity μ	
6	200 g	Iodine, 80 γ. Methylthio-uracil 5 mg	203 g	30.6 mg	7.5	++
6	210 g	Iodine, 80 γ. Methylthio-uracil 10 mg	219 g	36.2 mg	4.8	++(+)
12	200 g	Diiodotyrosine, 200 γ. Methylthio-uracil 5 mg	203 g	34.6 mg	4.9	++
11	214 g	Methylthio-uracil, 5 mg	215 g	36.8 mg	8.5	+++
10	203 g	Methylthio-uracil, 10 mg	213 g	39.6 mg	6.7	++++

Female rats of 6 months were treated with 5—10 mg methylthio-uracil daily (given through an esophageal tube, suspended in 1 ml water plus 5 % mucilage) through a period of 15 days. In the same period some of the animals were given iodine, 80 γ daily, in the form of potassium iodine dissolved in 1/2 ml water, or diiodotyrosine, 200 γ daily in

aqueous basic solution (pH: about 11). The solutions of potassium iodide and diiodotyrosine were given subcutaneously on the back of the animal. 24 hours after the last dose, the animals were killed with gas (after being weighed); the thyroid was removed, weighed and prepared for histological examination as described in Chapter II. The findings are recorded in Table 34.

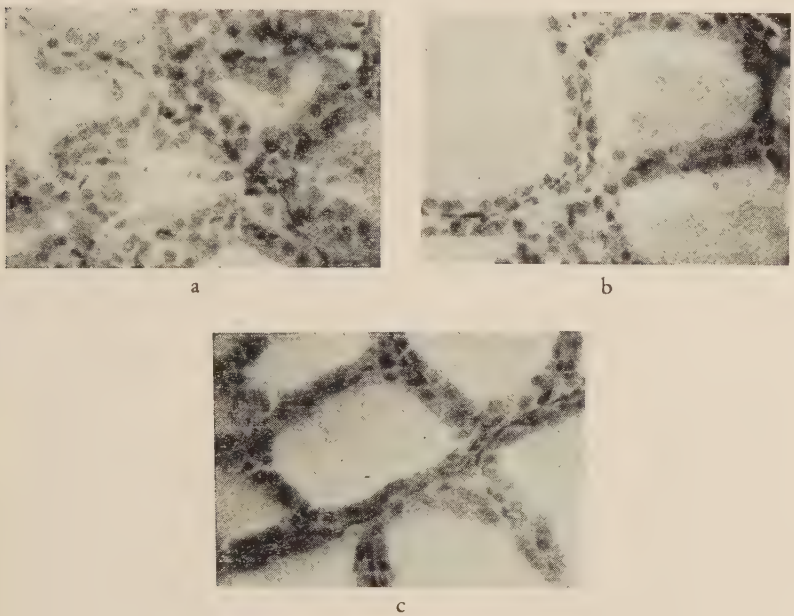


Fig. 31. Microphotos of thyroids from female rats treated with:
a. — 5 mg methylthio-uracil daily for 15 days.
b. — 5 mg methylthio-uracil + 80 γ iodine daily for 15 days.
c. — 5 mg methylthio-uracil + 200 γ diiodotyrosine daily for 15 days.
(Magnif. × 400.)

Histological Examination. — The thyroids removed showed that the very pronounced histological activity induced in rats under treatment with 5 or 10 mg methylthio-uracil for 15 days was attenuated quite considerably when the animals at the same time were given iodine in the form of potassium iodide or diiodo-

tyrosine. This effect of iodine manifests itself by a rather considerable accumulation of colloid in the thyroid, together with flattening of epithelial cells of the follicles (cf. Fig. 31). Under the present experimental conditions no difference can be demonstrated in the effect of potassium iodide and of diiodotyrosine. When the dose of methylthio-uracil was increased from 5 mg to 10 mg while no change was made in the amount of iodine given, there was an increase in the histological activity of the thyroid. It is to be emphasized that within the various groups of experimental animals there was a high degree of consistency in the thyroid changes encountered in the individual animals belonging to the respective groups.

In addition it will be noticed that under the experimental conditions here employed the supply of iodine is able to reduce the size of the goiter even though in a very slight degree.

Mackenzie & Mackenzie[121] and *Kjerulf-Jensen*[97] have arrived at concordant results. But, in addition, *Kjerulf-Jensen* has been able to demonstrate that administration of iodine is able to prevent the strumogenic activity of small doses of methylthio-uracil to such an extent that the glandular tissue remains normal histologically, nor does any definite goiter develop.

Okkels & Krogh[151] have further been able to show that supply of iodine to guinea-pigs under treatment with thyrotropic hormone causes a decrease in the metabolism almost to normal values accompanied by evidence of decreasing histological activity of the thyroid, whereas the Golgi apparatus remains hypertrophic, which is explained as attributable to the continuous stimulation of the thyroid by the thyrotropic hormone.

The observations mentioned here suggest that the action of iodine and of thyrotropic hormone set in at different points — something that has been emphasized indeed also by *Kjerulf-Jensen*[97]. In this connection it is to be mentioned that *Williams, Weinglass & Kay*[207] have been able to show experimentally that the thio-uracil concentration in the guinea-pig thyroid decreases on simultaneous supply of thyrotropic hormone, while it increases on administration of iodine.

The experiments further show that, in spite of simultaneous

treatment with methylthio-uracil, the thyroid still absorbs iodine.

The iodine absorption by the thyroid does not proceed in a normal manner, however, when the thio-uracil effect asserts itself at the same time. Thus *Keston, Goldsmith et al.*[96] have been able to show that in rats under treatment with thio-uracil the thyroid does not absorb very much injected radio-active ("marked") iodine — something which these investigators were able to confirm also through experiments in vitro. Finally, *Rawson, Evans et al.*[155] found that the accumulation in the thyroid of inorganic "marked" iodine is greatly lowered in patients under treatment with thio-uracil, whereas its excretion with the urine is increased.

It may be that a decrease in the iodine absorption by the thyroid under thio-uracil treatment may contribute in a slight degree to the changes in the gland from the thio-uracil effect. But, other factors seem to play a greater role in this respect.

According to *Harington*[70] the conversion of diiodotyrosine to thyroxin may be carried through experimentally in vitro with pieces of tissue from the thyroid; but if the thyroid tissue has been homogenized, this conversion does not take place. From this observation *Harington*[70] concludes that an intracellular enzymic system is contributory to this conversion; and, furthermore, he had made it rather probable that this conversion takes place through oxidizing processes. *Schachner, Franklin & Chaikoff*[169, 170] have likewise been able to show in vitro that oxidizing processes take a part in the formation of diiodotyrosine as well as thyroxin; and these investigators have further shown that the processes of conversion are inhibited by oxygen insufficiency — something that applies also to substances inhibiting the effect of cytochromic oxidase (cyanide, azide, sulphide). From their studies the authors arrived at the conclusion that the production of diiodotyrosine as well as of thyroxin by the thyroid "is linked with aerobic oxidations in which the cytochrome-cytochrome oxidase system is involved."

Furthermore, in experiments carried out in vitro, *Franklin & Chaikoff*[50, 51] have been able to show that sulfanilamide, sulfapyridine, sulfathiazole and sulfaguanidine in weak concentrations

are able to inhibit the formation of diiodotyrosine and thyroxin in the thyroid gland. The authors emphasize that, in this weak concentration, sulfanilamide does not particularly inhibit the iodine-concentration capacity of the thyroid and that the effect of the substance does not exert itself fully until the iodine has been absorbed by the thyroid, so that its inhibitory effect manifests itself particularly in the conversion of inorganic iodine to diiodotyrosine as well as thyroxin. The degree of this inhibition is relative to the concentration of the substance.

The way in which this inhibitory influence asserts itself is still unknown. *Schachner, Franklin & Chaikoff*[170] state, however, that the inhibitory effect of sulfanilamide is not of the same nature as the above-mentioned effect on cytochromic oxidase. On the other hand, *Dempsey*[37] has shown that thio-uracil is able to inhibit the peroxidase activity in the thyroid, and he thinks that a decrease in the peroxidase activity will interfere with the conversion of diiodotyrosine to thyroxin. *Rawson, Evans et al.*[155] hold the view that thio-uracil effectuates a blockade of the enzymic systems in the thyroid which are essential to iodization of thyroprotein, so that the result will be a formation of a physiologically inactive product.

(Here, in passing, it may be mentioned that in May 1944 the writer collected a considerable amount of frog eggs which were distributed together with aquarian plants over a good many glass vessels. The purpose of this was to observe the effect of quite weak thio-uracil concentrations on the development of the frog eggs to tadpoles and their metamorphosis. Some rather serious accidents in connection with the German occupation of our country disturbed the course of the experiments, and the eggs died — and as this happened in the month of June no additional eggs could be collected that year.)

The observations mentioned above show that thio-uracil inhibits not only the iodine absorption by the thyroid but also the formation of the thyroid hormone itself, which then will show a deficit in the thyroid. In keeping herewith *Mackenzie & Mackenzie*[121] state that the thyroid colloid in their treated animals has been poor in iodine; and *Rawson, Evans et al.*[155] have been able further

to show that the physiological activity of thyroid given to myxedematous patients is lowered after thio-uracil treatment.

It seems reasonable to assume that the amount of thyroid hormone in the organism will be lowered at the same time as the formation of this hormone in the thyroid is inhibited. *Morton, Chaikoff et al.*[139] have been able, however, to show that 30 % of radio-active iodine given to thyroidectomized rats was demonstrated after 3 days in organic compounds — two-thirds of it in the form of diiodotyrosine, one-third as thyroxin. These investigators have made sure that the thyroidectomy was complete; furthermore, they were able from the animals to isolate diiodotyrosine as well as thyroxin in crystalline form. Thus, the possibility must exist: that thyroxin may be produced outside the thyroid, but where and how this thyroxin formation takes place, is still unknown.

The studies presented here (see Chapter VI) have shown, however: 1) that treatment with methylthio-uracil may reduce the metabolism in rats to the level of thyroidectomy; and 2) that in already thyroidectomized rats no additional fall in the rate of metabolism is obtained by additional treatment with large doses of methylthio-uracil. These observations show that the thyroxin formed outside the thyroid must be physiologically inactive; or, if this thyroxin is physiologically active, the treatment with thio-uracil has no inhibitory effect on its formation, so that it keeps on exerting its effect in the organism. Finally, the experiment indicate that by means of methylthio-uracil it is possible completely to block the formation of thyroid hormone in the thyroid.

So it can be taken as fairly established that the amount of thyroid hormone in the organism of the treated animals is lowered by the administration of thio-uracil. According to the observations reported in Chapter IX, this implies that the state of equilibrium between this hormone and the thyrotropic hormone of the anterior pituitary is disturbed, resulting in an overproduction of thyrotropic hormone.

Most of the authors cited here, indeed, subscribe to the view that a compensatory overproduction of thyrotropic hormone is the

cause of the thyroid changes here mentioned. *Gordon, Goldsmith & Charipper*[61] found, however, a decrease in the thyrotropin content of the serum and pituitary from rats that were treated with thiourea or sulfadiazine, while they state that the excessive amount of thyrotropin produced is removed by the thyroid (cf. Chapter IX, p. 127).

Evidence supporting the view that the thyrotropic hormone of the anterior pituitary lobe is responsible for the thyroid changes here obtained, is found in the fact that these changes fail to appear when the strumogenic substance are given to hypophysectomized animals (*e. g., Mackenzie & Mackenzie*[119], *Kennedy & Purves*[95] *Freiesleben et al.*[53]).

Also the writer has carried out an experiment in which an attempt was made to give methylthio-uracil (5 mg daily for 15 days) to 7 rats, on which a colleague obligingly had performed hypophysectomy. It turned out, however, that after this experiment the thyroid weight was normal only in 1 rat, whereas it was increased in the remaining 6 rats, even though by no means in the same degree as observed in normal rats under the same treatment. Correspondingly, in all the animals in which the thyroid weight has been increased it was possible macroscopically to demonstrate remnants of the pituitary, whereas no such remnants could be demonstrated in the rat that showed a normal thyroid weight.

Like hypophysectomy, administration of thyroxin or dried thyroid substance may prevent the appearance of thyroid changes in rats that are treated with strumogenic substances.

In an experiment with female rats, 6 months old, that were given 5 mg methylthio-uracil daily, by means of an esophageal tube plus 20 γ thyroxin (given subcutaneously in aqueous basic solution) the writer was not able at the conclusion of the experiment to find any evidence of an increased histological activity of the thyroid. On the contrary, slight evidence of the histological activity usually found in the controls had decreased or even disappeared completely, and the average thyroid weight for these animals was lower than the average for the controls (11.9 mg as against 13.4 mg in the controls).

Something similar has been reported by *Astwood*[15], *Freiesleben et al.*[53], *Mackenzie & Mackenzie*[121]. Furthermore, *Mackenzie & Mackenzie*[121] also found that thyroxin or dried thyroid substance reduces the thyroid weight in the animals to subnormal values.

From the experiment it may be concluded that thio-uracil has no effect on the finished thyroxin or thyroid hormone. On the other hand, it cannot yet be decided whether the effect of thyroxin here may be due to the circumstance that it covers the thyroid hormone deficit of the organism and thus, possibly may be identical with this (cf. *Harington*[70]), or whether it be a matter of direct effect on the thyroid or, possibly an inhibition of the normal production of thyrotropic hormone by the anterior pituitary. In this connection *Williams & Bissell*[203] have been able to show that the physiological activity of dried thyroid substance given to myxedematous patients is not impaired by the simultaneous administration of thio-uracil.

When thio-uracil treatment has no effect on any completed formation of thyroid hormone, it seems obvious that the thio-uracil effect in the organism will not manifest itself till the reserve supply of thyroid hormone of the organism is exhausted. As mentioned already, this appears to explain the fact that guinea-pigs, which in themselves are rather sluggish, with a thyroid markedly filled with colloid fail to react to thio-uracil in some of the experiments recorded. If such experiments go on sufficiently long, however, there can be no doubt that the effect will manifest itself. Furthermore, *Astwood*[16] has been able to show that in man with a normal thyroid function the thio-uracil effect does not appear until the treatment has been going on for a long time. Finally *Mackenzie & Mackenzie*[119] state that when thyroid changes have not been reported in man treated with sulfanilamides, this may be due to the circumstance that man does not react exactly like rats, mice and dogs, being sensitive only to thio-urea. But, I think, it should be added that probably the treatment with sulfanilamides has never been so protracted that the antithyroid effect of these substances might manifest themselves clinically.

PART II.

CLINICAL STUDIES

Chapter I

INTRODUCTION. PURPOSE OF THE CLINICAL STUDIES. PATIENT MATERIAL

Introduction.

Means[135] briefly describes thyrotoxicosis as a "state of intoxication dependent on the thyroid". If this state is due to an increased output of normal thyroid hormone — which to-day is taken to be the case — the designation hyperthyroidism is serviceable. *Means*[135] employs the term "toxic goiter". Enlargement of the goiter needs not necessarily be present in thyrotoxicosis. To find the proper designation for this pathological state of the organism appears to be rather difficult, as is plainly evident from the works of several authors (*e. g., Means*[135], *Chvostek*[34]).

The clinical picture of this morbid state is well known, but its patho-physiological aspects include many problems, still unsolved, which, among other things, give rise to the uncertainty in our conception of the lesion.

To me it seems reasonable to adopt the term "thyrotoxicosis" as a common designation for all morbid conditions in the organism due to a hyperfunction of the thyroid.

The etiology of thyrotoxicosis is one of the great, as yet unsolved, problems, which has been discussed by numerous authors (*e. g., Eggert Møller*[142], *Sølling*[188], *Franck*[48], *Means*[135], *Chvostek*[34]) but none of the theories advanced so far has proved adequate.

Thus, a classification of the various forms of thyrotoxicosis after etiology is still out of the question. To make the pathologic-anatomical changes in the thyroid the basis of a classification is unsatisfactory and clinically unserviceable.

The clinical picture of thyrotoxicosis being subject to quite considerable variation, a classification after the clinical features is

difficult, and attempts at this have given rise to marked discrepancies.

In his comprehensive work of exophthalmic goiter, *Chvostek*[34] says that there are a number of clinical conditions resembling Basedow's disease more or less; and he designates these forms as hyperthyreosis, thyrotoxicosis or, simply, thyreosis. *Means*[135], employing the joint designation "toxic goiter" looked upon Graves' disease (= Basedow's disease = "exophthalmic goiter") and the Plummer type (= toxic adenoma or adenomatous goiter with hyperfunction) as the two extreme conditions of thyrotoxicosis, between which there are a number of intermediary types. *Redisch & Perloff*[159] claim, however, that any distinction between "exophthalmis goiter" and "toxic goiter" hardly is maintainable, in particular because exophthalmus is an exceedingly variable and inconstant symptom in hyperthyroidism.

One feature, however, is common to all the types of thyrotoxicosis, namely: hyperfunction of the thyroid with increased output of hormone, which again induces a number of symptoms characteristic of thyrotoxicosis, varying in frequency and intensity.

As mentioned already, the thio-uracil effect bears upon the synthesis of the thyroid hormone. In this connection, therefore, it does not matter whether the thyroid affection is of one type or another, whether it is primary or secondary in relation to other extrathyroid lesions, as long as the thio-uracil treatment proves effective.

But as the principal question to be dealt with here is demonstration of the thio-uracil effect on the state of hyperthyroidism, the aspects mentioned will naturally become topical if the thio-uracil effect fails to manifest itself. If this happens, we have to take into consideration the significance of extrathyroid factors to the symptoms and their persistence in spite of the treatment; and then thio-uracil may hardly exert its effect by way of the thyroid hormone.

In dealing with the question whether the action of thio-uracil has any curative effect on the thyrotoxicosis itself, we shall likewise have to consider the significance of possible extrathyroid factors to the development and persistence of thyrotoxicosis.

As to the thio-uracil effect on thyrotoxicosis, on the other hand, it is important to distinguish between primary and secondary forms in relation to a possibly preexisting change in the thyroid. For the thio-uracil effect is found as a rule to appear more rapidly in the primary forms turning up in a previously normal thyroid. Here as a rule the thyroid hyperplasia will be diffuse. In contrast hereto, the effect usually appears more slowly in the secondary forms, in which the thyroid previously has been the site of a non-toxic, diffuse or adenomatous hyperplasia. In this connection it is to be mentioned that, according to *Marine*[123] thyroid adenomas originally are induced by the same physiological stimulus as has produced the goiter in which they make their appearance.

The great variations in the symptoms of thyrotoxicosis naturally have given rise in the course of time to a great number of therapeutic methods aimed at various points. Detailed descriptions of these methods have been given by several authors (*e. g.*, *Chvostek*[34], *Means*[135], *Eggert Møller*[142], *Redisch*[158], *Redisch & Perloff*[159], *Sattler*[168]). Now, many of these therapeutic methods are merely of historical and theoretical interest, as they have been given up long ago. A few methods, however, have proved quite effective and valuable. This applies above all to: 1) iodine therapy, 2) X-ray treatment, and 3) partial thyroidectomy combined with iodine therapy. In addition, as a most important supplement to these therapeutic methods, we have dietary and vitamin treatment, fattening — if necessary, combined with administration of insulin — rest and, if possible, climatotherapy. *Chvostek*[34] further emphasizes the importance of this point: that the treatment is given by a physician equipped with a good deal of common sense so that he looks correctly upon the state of the patient, treating him calmly and rationally.

Any detailed account of these different methods of treatment would fall outside the scope of the present work.

The treatment of thyrotoxicosis with thio-uracil was commenced soon after the discovery of the specific effect of the strumogenic substances on the hormonal function of the thyroid.

At first thio-urea and thio-uracil were employed exclusively by the various authors; later, also methylthio-uracil has been adopted widely. As mentioned already, because of the toxicity of thio-urea I have never employed this substance clinically. Even though thio-uracil and methylthio-uracil sometimes may have rather serious untoward effects too, these substances have now quite displaced the use of thio-urea, which is more toxic and less effective. Many clinicians and authors are still rather skeptic with regard to the therapeutic employment of the substances mentioned — largely because thio-urea formerly has been employed to an all too great extent, but also on account of the question of dosage, which will be dealt with especially in Chapter V.

When thio-uracil therapy is to be tried out thoroughly in thyrotoxicosis, it is essential to try its employment in any form of this lesion and record exactly its effect on the highly varying clinical features of the lesion. As to the dosage, in spite of the experience gained, from the experimental-biological investigations we have to proceed tentatively in order to find the optimal dose in each individual case. Finally, it is of decisive importance to realize whether the untoward effects produced by the treatment be so frequent and of such a serious character that it becomes imperative quite to give up this form of treatment or to reduce its employment considerably.

Purpose of the Clinical Studies.

The clinical studies here reported were commenced at a time when the world war made the available literature on this question most limited, reducing it to a few examples of the favorable influence of thio-uracil and thio-urea on thyrotoxicosis.

After the first biological experiments, among others, on the toxicity of thio-uracil and thio-urea, in February 1944 treatment of thyrotoxicosis was commenced, whereas thio-urea was found to be too toxic for clinical use.

In April 1944 methylthio-uracil was adopted for the treatment of patients with thyrotoxicosis after experimental studies had proved that methylthio-uracil in rats had a stronger strumogenic

effect than thio-uracil, while its toxicity was only a little greater than that of thio-uracil.

Also phenylthio-uracil was tried in the clinic, but only in one case (cf. Fig. 36).

The purpose of the clinical part of this work has been:

1. To investigate the effect of thio-uracil on the thyrotoxic state in general and on the more important symptoms and sequelae of thyrotoxicosis *within the first year.*
2. To investigate the serviceability of thio-uracil for
   a) protracted treatment of thyrotoxicosis;
   b) preoperative treatment of thyrotoxicosis.
3. To estimate the thio-uracil effect on the entire organism with a special view to untoward effect.
4. To adjust the proper thio-uracil dosage.

As gradually a considerable literature has been published on the subject, the results obtained in these studies will finally be compared with those reported by other authors, enabling us with greater certainty to estimate the serviceability of thio-uracil in the treatment of thyrotoxicosis.

Patient Material.

From February 1944 to April 1945 altogether 54 patients were treated with thio-uracil or methylthio-uracil.

In two preceding papers[191, 192] an account has been given of a part of the patients to be mentioned here.

It will be appropriate first to give a survey of the total 54 patients treated in this way. It is to be emphasized at once that particular details will not be given here of all the individual patients, as this would take up too much space. Particular mention of the past and present history of the patients as well as the course of the illness will be given only whenever some special features assert themselves. Concerning the other patients, they may be said not to have presented any features of special interest apart from what will be mentioned here.

Owing to the lack of concordance in the literature with regard to the nomenclature of thyrotoxicosis, I have chosen briefly and simply to designate the lesion as thyrotoxicosis, without attempting any more detailed subdivision of its various forms, which, I think, would be of no particular interest here. Still, a few forms of thyrotoxicosis will be pointed out especially. This applies to the secondary form, which designation implies that demonstrable changes in the thyroid (goiter) have been present prior to the thyrotoxic state. Further, mention is made of thyrotoxicosis accompanied by exophthalmus and, finally, cases of recurrence.

Grouping of the patients:

Total number treated: 54 patients.

Thio-uracil: 12 patients, one of whom was later treated with methylthio-uracil.

Methylthio-uracil: 42 patients, one of whom had previously been treated with phenylthio-uracil; besides there is the above-mentioned patient who first was treated with thio-uracil.

Patients treated with thio-uracil:

11 women, aged 30—68 years.

1 man, aged 63 years.

Classification and duration of the lesion:

a. Thyrotoxicosis — primary: 9 patients, 3 of them with exophthalmus.

Duration of illness before treatment:

4 patients; 1—6 months.

5 patients; 6 months — 2 years.

b. Thyrotoxicosis — secondary: 3 patients, two of whom had had a noticeable goiter for 10 and 16 years respectively. The state of thyrotoxicosis had persisted for 2 months and 1 year respectively. One patient had had a nodular goiter for 5—6 years, and a heart lesion for the same length of time; duration of thyrotoxicosis unknown.

Duration of treatment:

a. Thyrotoxicosis — primary (9 patients):
   4 patients: 15, 14, 13 and 12 months, respectively. Treatment being continued.
   2 patients: 5 months and 1 month. Treatment discontinued on account of unsatisfactory results.
   3 patients: 10, 2 and 1 months, respectively; then subtotal thyroidectomy.

b. Thyrotoxicosis — secondary (3 patients):
   1 patient: 14 months. Treatment being continued.
   1 patient: 2 months, then discontinued on account of untoward effect. Shortly after, methylthio-uracil was tolerated well. So the treatment was continued with this remedy.

1 patient: 52 days, then subtotal thyroidectomy.

Patients treated with methylthio-uracil:

36 women, aged 21—71 years.
6 men, aged 41—61 years.

Classification and duration of the lesion:

a. Thyrotoxicosis — primary: 34 patients, 6 of them with exophthalmus.
   Duration of illness before treatment:
   17 patients: 1—6 months.
   11 patients: 6 months—2 years.
   2 patients: $>$ 2 years.
   4 patients: No definite data.

b. Thyrotoxicosis — secondary: 2 patients. One of them had had a recognizable goiter for about 5 years; the state of thyrotoxicosis had lasted for 1 year. The other patient claimed always to have had a goiter. The thyrotoxicosis had been present for 2 months.

c. Thyrotoxicosis — recurrent: 5 patients.
   1 patient: Treated in hospital for thyrotoxicosis about 7 years before. Since, slight symptoms of this lesion periodically; now gradual aggravation.

3 patients: Thyroidectomy respectively 15 months, 7 years and 17 years before. Thyrotoxicosis has persisted respectively for 4 months, 5 years and 17 years, in the latter two cases in varying degree.

1 patient: Symptoms of thyrotoxicosis 2 years before; they subsided spontaneously; now the state of thyrotoxicosis had persisted for 2—3 months.

d. Thyrotoxicosis from excessive intake of thyroidin.
1 patient (8 years' abuse of thyroidin). The state of thyrotoxicosis had persisted for 5 months.

Duration of treatment:

a. Thyrotoxicosis — primary (34 patients):
8 patients: 2—4 months.
9 patients: 5—10 months.
2 patients: 11—12 months.
Treatment being continued.
15 patients: Operation (subtotal thyroidectomy) after respectively 21, 25, 30, 31, 35, 37, 40, 50, 64, 76, 78, 119, 150, 238 and 291 days of treatment.

b. Thyrotoxicosis — secondary:
2 patients: Treated respectively 71 and 364 days.
Treatment being continued.

c. Thyrotoxicosis — recurrent:
5 patients: Treated respectively 61, 63, 65, 153 and 310 days. Treatment being continued.

d. Thyrotoxicosis from excessive intake of thyroidin:
1 patient treated for 366 days. Treatment being continued.

Finally, mention is to be made of 1 patient (woman with secondary thyrotoxicosis) in whom, after 2 months' treatment with thio-uracil, the treatment was continued with methylthio-uracil, with which she had been treated (at this writing) for 354 days. The treatment is still being continued.

Chapter II

CLINICAL EFFECT OF THIO-URACIL TREATMENT

As mentioned already, no particular account will be given of the individual cases, unless they present some features of special interest. Nor will any collective detailed description be given of the therapeutic results. On the other hand, the entire question about the clinical effect of thio-uracil treatment on thyrotoxicosis will be discussed — in successive sections — starting with the therapeutic results here obtained, which again will be compared with the results reported by other authors.

This procedure, I think, will make the whole question about the thio-uracil effect on the clinical state of thyrotoxicosis more readily surveyable, whereas it does not allow us to follow the effect obtained in the individual cases — something which unfortunately will be necessary in this connection where a brief general estimation of the therapy is aimed at.

The first question to be dealt with is the clinical effect of thio-uracil treatment on thyrotoxicosis in general.

Writer's Material:

54 patients treated with thio-uracil or methylthio-uracil.

Treatment effective in 47 patients.

Treatment ineffective in 7 patients.

It will be appropriate briefly to mention these 7 patients, 3 of whom were treated with thio-uracil, 4 with methylthio-uracil.

Treatment ineffective:

Patient No. 3. Man, 63 years old.

Diagnosis: Thyrotoxicosis (Myocardial degeneration and dilatation of the heart; arrhythmia perpetua).

Past history of fairly good health. For the last 10 years, marked enlargement of the thyroid, but never inconveniencing. During the last 2 months, increasing thyrotoxic symptoms.

Iodine therapy given for 38 days, without any effect whatever. Then thio-uracil was given in fairly large doses, but the result was an aggravation of the thyrotoxicosis.

After 36 days, iodine was given again — this time together with thio-uracil — which was followed by rapid improvement.

Further mention of this patient is made in Chapter IV, with curves for the metabolism, weight and dosage (see Fig. 52).

Patient No. 26. Man, 51 years old.

Diagnosis: Thyrotoxicosis (arterial hypertension).

Past history of fairly good health. In the last 3 months increasing symptoms of thyrotoxicosis.

Methylthio-uracil (0.8—1.0 g) was given for 30 days. Under this treatment, the rate of metabolism was 135 — 135 — 137 — 143 — 131 %. Weight falling from 80.2 to 78.2 kg.

No effect from this treatment, whence it was discontinued.

Then improvement under iodine treatment. Thyroidectomy.

Patient No. 19. Woman, 65 years old.

Diagnosis: Thyrotoxicosis (cardiac disease, arrythmia perpetua; bronchitis).

Past history of fairly good health. For the last 2 years, slight symptoms of thyrotoxicosis.

Methylthio-uracil treatment (0.6 g daily) was instituted. After 21 days this treatment was discontinued on account of rise in temperature. The thyrotoxic symptoms kept unchanged during the treatment, but the rate of metabolism rose from 140 to 166 %.

Then iodine therapy and operative treatment.

Patient No. 7. Woman, 63 years old.

Diagnosis: Thyrotoxicosis, slight degree (mitral stenosis, compensated; nervosism).

Metabolism: + 20 %.

Thio-uracil treatment (1.2 g daily) for 4 weeks, under which the mild thyrotoxic symptoms persisted, and the metabolism remained unchanged, wherefor this treatment was discontinued, and X-ray treatment was given.

6 months later: the slight thyrotoxic symptoms were a little less pronounced, but the metabolism was still about + 20 %.

Patient No. 11. Woman, 68 years old.

Diagnosis: Thyrotoxicosis, slight degree (angina pectoris; nervosism).

Metabolism: + 20 to + 30 %.

Thio-uracil was given for 157 days (commencing with 1.2 g and decreasing to 0.8 g daily).

Under this treatment there were several periods of improvement, with metabolism from about 0 to + 10 %, but the mild symptoms kept recurring every time, and the metabolism rose again to about + 20 %. The weight remained unchanged.

All told, no definite effect from the treatment, which then was discontinued, and X-ray treatment was given.

Patient No. 51. Woman, 43 years old.

Diagnosis: Thyrotoxicosis, slight degree? (Cardiac disease; pulmonary silicosis, pronounced).

After working in a silver-plate factory for 21 years, the patient was granted a disablement benefit (7 years ago) on account of pulmonary silicosis. During the last 3 years, increasing cardiac symptoms.

Neither the past history of the patient nor the physical examination gave any definite evidence of thyrotoxicosis, but the metabolism kept constantly between + 20 % and + 40 %, on which account the patient was treated with methylthio-uracil (0.6—0.8 g daily) for 58 days. Then 2 applications of X-rays were given; and, after 2 months, methylthio-uracil treatment (0.4—0.6 g daily) was repeated for 3 weeks. The metabolism remained quite refractory to the treatment, keeping at a level between + 20 % and + 40 %. The weight remained unchanged.

Patient No. 38. Woman, 29 years old.

Diagnosis: Thyrotoxicosis, slight degree (metrorrhagia; cancer of the uterus).

For about 1 year, nervousness and slight enlargement of the thyroid. During the last 3 months metrorrhagia. Cancer of the uterus was ascertained, and the patient was treated with radium. The slight thyrotoxicosis was treated with methylthio-uracil (0.6 g daily). After 26 days' treatment with this remedy the thyroid became swollen and tender, and the temperature rose to 38.5. The treatment was continued with 0.2 g methylthio-uracil, and the temperature returned to normal, while the tenderness of the thyroid subsided, but the goiter got a little larger, though without giving rise to any symptoms of compression.

After 108 days of treatment with methylthio-uracil, the slight thyrotoxic symptoms remained practically unchanged. The metabolism kept constantly at about + 20 %, and the weight kept unchanged.

As to the lack of effct from the thio-uracil treatment in the 7 patients here mentioned, it is to be pointed out that in the first 4 cases the duration of the treatment (21—36 days) has been too

short to allow of any decisive conclusions concerning the effect of the remedy in these patients.

In Case 51 the diagnosis of thyrotoxicosis is very dubious. Possibly the increased rate of metabolism in this patient has been due to extrathyroid conditions rather than to a hyperfunction of the thyroid. It may be that the pronounced cardiac and pulmonary lesions in this patient may have played a rôle in the increase of the metabolism. Indeed, we may feel tempted to think that something similar also applies more or less to Case 7 and, especially, Case 11, in which a heart lesion was present too.

Discussion.

In a patient, who also was suffering from a heart lesion, *Rose & McConnell*[164] observed a very slow effect of thio-uracil, but they also state that the presence of thyrotoxicosis in this case was not absolutely unquestionable. Similarly *Palmer*[152] mentions 2 patients with hypertension, poor kidney function and increased metabolism (averaging + 46 %). In these two patients a very protracted thio-uracil treatment lowered the metabolism to + 10 %, whereas it had no effect on the clinical features of the cases. Finally *Astwood*[16] has reported 2 patients with hyperthyroidism as a part of the syndrome of acromegaly; both patients were also suffering from hypertension and cardiac disease. In one of these patients the thio-uracil treatment showed some effect, but the metabolism did not return to a normal rate — in spite of the large doses given. In the other patient there was no effect on the metabolism and no clinical improvement in spite of intermittent treatment with thio-uracil, 0.3—0.6 g daily for 8 months. *Astwood*[16] says that perhaps the thyrotoxicosis contributed but slightly to the increased metabolism, and that the increased oxygen consumption possibly to a large extent was due to the heart lesion in this patient or to some other metabolism-stimulating factor.

If, in a given case, the increased metabolism is due to thyroid hyperfunction but in a slight degree — or not at all — we can only expect the thio-uracil effect to manifest itself but slowly, as in such cases the thyroid may contain a reserve amount of its specific hormone. This is in keeping with the observation made

by *Astwood*[16] on patients with normal thyroid function: that it requires a rather protracted treatment with thio-uracil before its effect on the organism asserts itself.

As to our patient No. 38, I am not able to offer any explanation of the lack of thio-uracil effect.

In 47 patients the thio-uracil treatment gave the expected effect, completely or partially, on the thyrotoxic state of the patients, *i. e.*, in 87 % of the total patient material.

For the sake of comparison, in Table 35 the clinical effects of thio-uracil and methylthio-uracil (also thio-urea) on thyrotoxicosis are entered as reported by various authors. In this connection, the

TABLE 35.

Clinical Effectivity (complete or partial) of Thio-uracil Therapy in Thyrotoxicosis as reported by Various Authors.

Author	Number of patients	Remedy given: a: Thio-uracil b: Methylthio-uracil c: Thio-urea	Effectivity +	0
Astwood[16]	51	a	51	0
Alsted & Lindholm[6]	4	a	4	0
Bartels[18]	11	a	11	0
Bartels[19]	64	a	64	0
Donald & Dunlop[39]	31	a	30	1
Eaton[42]	40	a	39	1
Espersen & Roholm[44]	7	c	7	0
Frisk[55]	23	a+b+c	23	0
Himsworth[78]	32	a(+c)	32	0
Jackson[83]	30	a	30	0
Mc Gavack *et al.*[118]	26	a	26	0
Meulengracht & *Scmith*[137]	77	b	77	0
Newman *et al.*[146]	6	a	6	0
Nussey[148]	27	a	26	1
Palmer[152]	50	a	50	0
Paschkis *et al.*[153]	21	a(+c)	20	1
Rawson *et al.*[155]	19	a	19	0
Rose & Mc Connel[164]	36	a	34	2
Westergaard[199]	22	b	19	3
William[200]	9	a	6	3
Williams & Bissell[203]	9	a	9	0

important point is whether or not thio-uracil has any effect; a distinction between complete or partial effect is of minor importance, as this implies merely a difference in degree depending on various extraneous circumstances.

In 6 of the 12 patients, entered in Table 35, who did not respond to the treatment, this failure was due to the period of treatment being too short, among other reasons, because of untoward effects. In one patient who had been given iodine therapy for a long time no effect was seen after thio-uracil treatment for about 40 days. In view of the iodine therapy, in this case, too, the observation period has to be reckoned as too short.

1 patient was suffering from severe thyrotoxicosis together with diabetes mellitus, which was secondary in relation to the thyrotoxicosis.

1 patient, suffering from thyrotoxicosis + diabetes mellitus, had been treated with iodine for 6 years.

In 1 patient there appeared a considerable enlargement of the thyroid with hemorrhages in the gland, on which account the patient was given operative treatment.

In the cases of 2 patients no particulars are given with a view to the ineffectivity of the thio-uracil treatment.

Besides the authors cited in Table 35, several other clinicians have employed antithyroid substances in the treatment of thyrotoxicosis. Some of these works, however, have not been available to me; in other works no data are given as to the number of patients in whom the treatment has been effective.

In most of the patient materials cited above the cases are not classified, all forms of thyrotoxicosis being included.

From the findings mentioned above it seems justified to conclude that, if a sufficiently long treatment is practicable, thio-uracil is able to check the state of thyrotoxicosis completely or partially in more than 90 % of all patients suffering from this lesion.

Chapter III

POINT OF TIME FOR THE APPEARANCE OF THE THIO-URACIL EFFECT

In the preceding chapter it is shown that the clinical effect of thio-uracil in cases of thyrotoxicosis on the whole is very great, a decidedly favorable effect being obtained in more than 90 % of all thyrotoxicotic patients treated in this way. This does not necessarily mean, however, that thio-uracil treatment is able in just as many cases to make the thyrotoxic symptoms subside completely; indeed, this seems not to be the case. This question will be dealt with later.

The point of time for the appearance of the thio-uracil effect in thyrotoxicosis is a question of rather great importance, in the judging of which a good many aspects have to be taken into consideration.

All the patients in the present material were treated in hospital, none of them at home under their customary conditions of life. Now, it is a well-known fact that the mere confinement to bed and rest in a hospital often have a favorable influence on the state of thyrotoxicosis. Furthermore, as a rule, the patients are given sedatives immediately after their admission.

To take the patients' own judgement of the condition as the basis for the first appearance of the thio-uracil effect would be out of the question. Patients with thyrotoxicosis often show a somewhat peculiar and unstable mental habitus, and often they are lacking in a marked degree the proper recognition of their illness. According to *Sattler*[168] psychic changes constitute one of the most constant symptoms in these patients. So, when the patients learn that they are submitted to a new method of treatment, this knowledge may readily further influence their judgement of their con-

dition. Of course, it is a different matter when it comes to recognize that a complete change has taken place in the state of health.

Sattler[168] states that the most essential and most characteristic symptoms of Basedow's disease are: 1) rapid pulse, palpitation, and increased pulsation in the cervical vessels; 2) enlargement of the thyroid; 3) bilateral exophthalmus; and 4) tremor. Besides, he emphasizes that vasomotor disturbances (*e. g.*, flushing of the skin and sensation of heat) are a very frequent symptom; increased perspiration is one of the most frequent. Also digesting disturbances are important and frequent symptoms.

In estimating the appearance of the thio-uracil effect it is a serviceable procedure to use the effect on one or, preferably, some of the above-mentioned symptoms as criteria — that is, if they have been present. But, this procedure — a clinical judgement of the state of the patient — requires that the patient is watched very closely by the same physician and, preferably, several times daily. For several reasons, however, it has not been possible for me to meet this requirement to any sufficient extent, on which account I have adopted another procedure for this purpose.

Sattler[168] emphasizes that the metabolic disturbance is one of the most constant and most important symptoms of the lesion that often leads on to emaciation, in spite of abundant intake of food. For estimation of the first appearance of the thio-uracil effect, therefore, I have chosen the decrease in the rate of metabolism and the gain in weight as criteria of the appearance of the effect and to supplement these with the clinical judgement of the state of the patient.

Thus in order to be able to assert that the thio-uracil effect has become manifest in a patient with thyrotoxicosis it generally takes a noticeable and continuous decrease in metabolism accompanied by a distinct and continuous gain in weight, taking the other clinical features into consideration too. Some patients, however, have shown no particular gain in weight, in spite of a marked decrease in metabolism and a noticeable improvement in the general condition of the patient. In one patient there has not yet been any decrease in metabolism, although there is a marked gain in weight,

and the complaints of the patient are subsiding. In such cases the behavior of the metabolism or the body weight, together with the other clinical features have been decisive of the estimate.

This estimation is bound to be a matter of judgement, as the

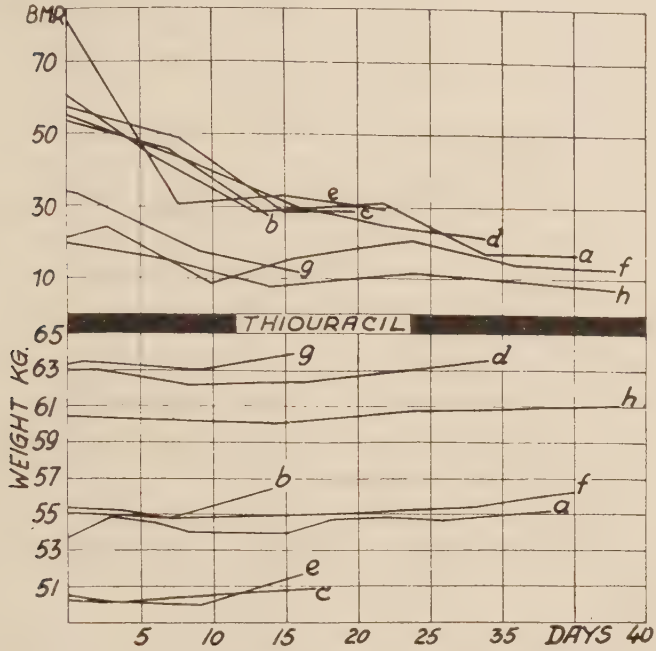


Fig. 32. Curves for the body weight and metabolism in 8 patients treated with thio-uracil (as to the small letters, see the text).

effect of the treatment appears gradually. Here, however, I have not been content with the first vague signs but insisted upon pronounced evidence of the effect.

As to the dosage, the reader is referred to Chapter V.

Writer's Material.

Thio-uracil: In 9 out of 12 patients treated with this remedy it had an unquestionable effect on the state of thyrotoxicosis. One of these 9 patients — a woman, aged 40, with a very severe degree of thyrotoxicosis had been under hospital treatment prior to the

thio-uracil therapy for no less than 19 months (in the same department), to no avail. In the case of this patient the thio-uracil treatment had an almost miraculous and — as far as may be judged — life-saving effect, on which account it will be appropriate to make particular mention of her case record (see p. 197). In the remaining 8 cases the thio-uracil treatment was instituted 5—15 (on an average, 9) days after admission to the hospital.

The effect of the thio-uracil treatment on the metabolism and weight of these 8 patients are presented graphically in Fig. 32.

In these 9 patients the thio-uracil effect could be recognized indisputably after a varying number of days (the following letters refer to the curves for the patients concerned in Fig. 32), namely: a, 31 days; b, 14 days; c, 15; d, 29; e, 15; f, 30; g, 16; and h, 38 days, while in the above-mentioned patient the effect appeared after 40 days of treatment.

Of these patients 4 (b, c, e, g) had a primary, moderate, untreated thyrotoxicosis, without any complicating heart lesion. In these patients the thyrotoxicosis had persisted respectively for 8 months, 18 months, 2 years, and 3 months.

Two patients (a and d) were suffering from a secondary thyrotoxicosis, the enlargement of the thyroid having lasted respectively for 5 and 16 years; in addition, there was a complicating heart lesion in case a.

One patient (h) had had a fairly mild degree of thyrotoxicosis for 1 year and had been given X-ray treatment twice — 6 and 3 months before — without any particular effect.

One patient (f) had a very slight degree of thyrotoxicosis that had been present only for about 1 month.

Methylthio-uracil. Of altogether 42 patients treated with methylthio-uracil, the remedy was effective in 38. In order to make the conditions of these patients more easily surveyable, I have divided them into three groups.

Group I:

16 patients with primary, untreated thyrotoxicosis without complicating heart lesion. In these patients the thyrotoxicosis had persisted respectively for 1, 1, 2, 3, 3, 3, 4, 6, 6, 10 months, 1, 1½,

1—2, 1—2, and over 2 years, while in 1 patient the duration of illness could not be established.

The treatment was commenced 4—23 (on an average, 9) days after admission.

The effect of methylthio-uracil therapy on the metabolism and body weight is presented graphically in Fig. 33.

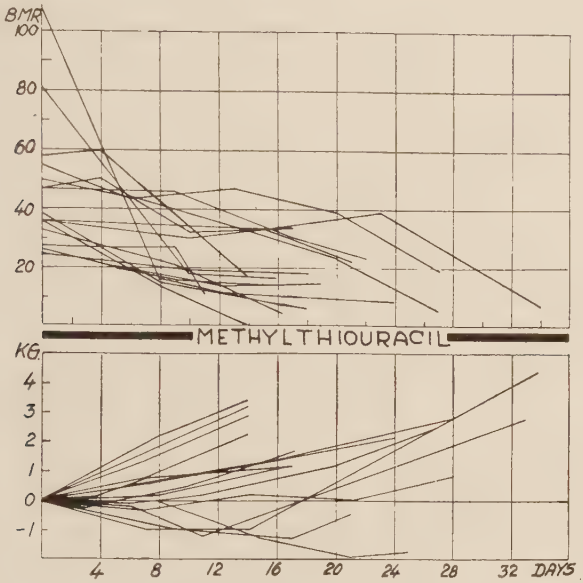


Fig. 33. Curves for the body weight and metabolism in 16 patients treated with methylthio-uracil.

In these 16 patients the effect of the treatment could be recognized with certainty, respectively after 15, 10, 12, 15, 20, 14, 20, 25, 15, 20, 15, 19, 17, 16, 14, and 21 days of treatment with methylthio-uracil (averaging 16 days), which corresponds fairly closely to the results in the similar group treated with thio-uracil.

Group II:

10 patients treated with iodine immediately before the institution of methylthio-uracil therapy. In these patients the thyrotoxicosis had persisted respectively for 2, 3, 4, 6, 6, 6, 9 months, 1—2 and

> 2 years, while in one patient its duration could not be established.

The treatment with methylthio-uracil was commenced 3—59 days after admission (on an average, 22 days). Some of the patients had been given iodine for a considerable length of time prior to the admission.

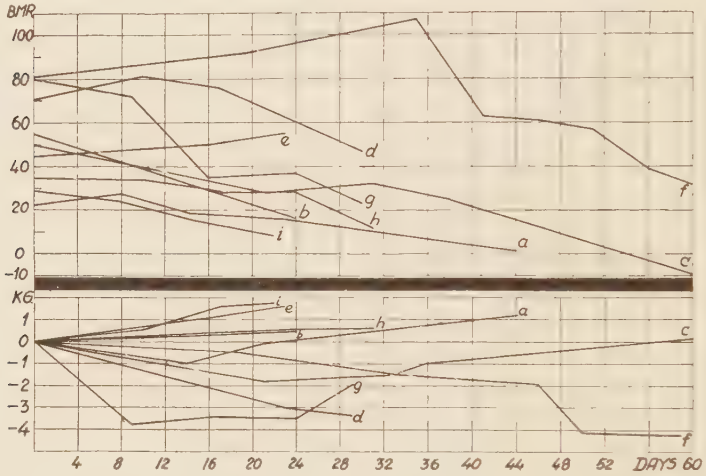


Fig. 34. Curves for the body weight and metabolism in 9 patients treated with methylthio-uracil after iodine therapy (as to the small letters, see the text).

The curves for the metabolism and weight of one of these patients are given in Fig. 53.

The effect of the treatment on the rate of basal metabolism and weight in the remaining 9 patients is shown in Fig. 34.

In these 10 patients the effect of the methylthio-uracil treatment could be recognized with certainty after a varying number of days (the following letters refer to the curves for the various patients in Fig. 34), namely: a, 21 days; b, 24 days; c, 36 days; d, 30; e, 23; f, 56; g, 30; h, 30; and i, 22 days. In the above-mentioned patient (Fig. 53) the effect appeared after 67 days of treatment. Thus the average time for the appearance of the effect was 33 days.

Group III:

12 patients treated with methylthio-uracil, including:

2 patients with secondary thyrotoxicosis (a, b); enlargement of the thyroid had been present for 5 and 15 years respectively;

4 patients with recurrence (c, d, e, f), c and d after 2 and 7 years respectively; e operated 6 years before; f operated 17 years before, (but recurrence of thyrotoxicosis 4 years before);

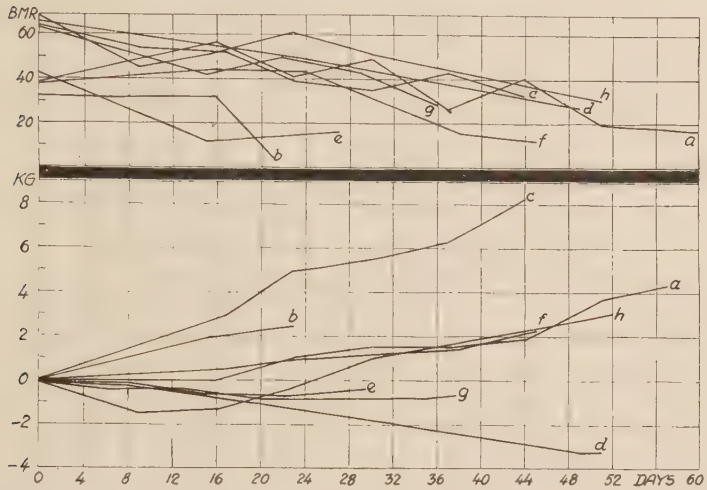


Fig. 35. Curves for the body weight and metabolism in 8 patients treated with methylthio-uracil (as to the small letters, see the text).

2 patients (g, h): thyrotoxicosis with complicating heart lesion (myocardial degeneration, arrhythmia perpetua).

In these 8 patients the thyrotoxicosis had been present for the following period: a, 1 year; b, 2 months; c, 4 months; d, uncertain; e, about 5 years; f, uncertain; g, 6 months and h, 3 months. In these cases the treatment with methylthio-uracil was instituted 5—27 days after admission.

The effect of this treatment on the metabolism and weight of the patients is recorded in Fig. 35.

In these 8 patients the effect of the methylthio-uracil treatment could be recognized with certainty after a varying number of days (the following letters refer to the curves for the respective pa-

tients in Fig. 35), namely: a, 60 days; b, 20 days; c, 44; d, 33; e, 25; f, 38; g, 35; and h, 30 days.

In 4 cases the first appearance of the methylthio-uracil effect could not be established because of interference of other factors:

Patient No. 34. Woman, 36 years old.

Moderate thyrotoxicosis for about 10 months.

After 2 weeks' treatment with methylthio-uracil, the patient had an exanthema and edema of the skin, on which account *the treatment was discontinued* temporarily.

During the first 2 weeks the rate of metabolism decreased noticeably, and the weight increased, but the other thyrotoxic symptoms kept quite unchanged.

After 5 days, methylthio-uracil was given again, but the untoward effect recurred, though in a milder degree.

As the therapeutic result was not satisfactory after 3 months of treatment, thyroidectomy was performed.

Patient No. 54. Woman, 54 years old.

Fairly slight degree of thyrotoxicosis together with marked obesity (94 kg) and heart lesion (paroxysmal arrhythmia perpetua).

The patient was first treated with rest in bed and reducing diet for 3 weeks, then with *estrin* in large doses for 1 month — without any particular effect. Then she was given methylthio-uracil which rapidly made the thyrotoxic symptoms subside. After 3 months, this treatment was discontinued, and then the symptoms recurred. Later, methylthio-uracil was given again for 3 months, but the therapeutic result was not satisfactory, on which account thyroidectomy was performed.

Patient No. 53. Woman, 47 years old.

Moderate primary thyrotoxicosis for about 7 months.

The patient was first given *phenylthio-uracil,* 0.6 g daily, for 42 days. Under this treatment the thyrotoxic symptoms subsided somewhat, but the condition of the patient was not satisfactory, and the increased metabolism kept rather unchanged, on which account phenylthio-uracil was discontinued and replaced with methylthio-uracil, which very soon (within about 1 week) made the thyrotoxic symptoms disappear completely and the metabolism decreased to a normal level (see Fig. 36). The treatment with methylthio-uracil is continued.

Patient No. 50. Woman, 47 years old.

Obesity and slight thyrotoxicosis that had lasted for 4 months and developed after intake of thyroidin for 8 years, sometimes in very large doses. Now she was treated with reducing diet and methylthio-uracil, to which the thyrotoxic symptoms yielded but slowly.

Under the continued treatment with methylthio-uracil it was found necessary — because of her gain in weight (over 10 kg) — in this patient to lower the dose. But then the thyrotoxic symptoms returned, though in a lesser degree, and the rate of metabolism kept at a slightly elevated level.

Finally it is to be mentioned that in the case of one patient (Fig. 32, a) the administration of thio-uracil had to be discontinued on account of untoward effects. A little later, the patient was given methylthio-uracil,

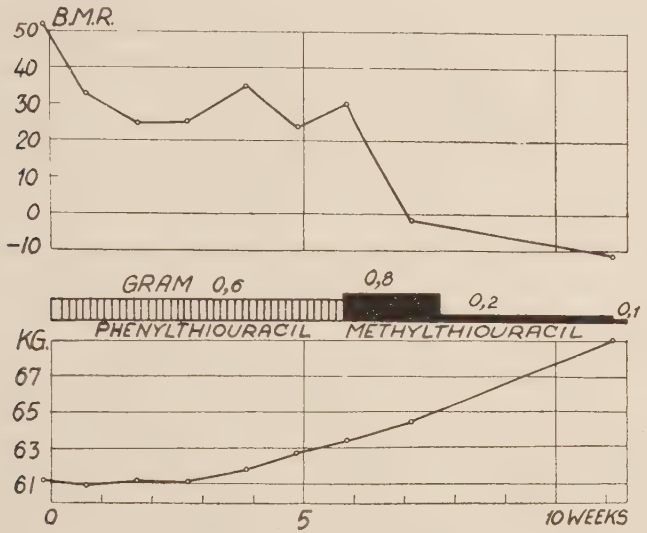


Fig. 36. Curves for the body weight and metabolism in a woman, 47 years old, treated with phenylthio-uracil and methylthio-uracil (see the text).

which was tolerated well. A more detailed mention of this patient, No. 1, will be given later (see Fig. 59).

Discussion.

There appears not to be any decisive difference in the effect of thio-uracil and methylthio-uracil. Taking into consideration, however, that, as a rule, methylthio-uracil was given in smaller doses than thio-uracil in the cases mentioned here (cf. Chapter V), we may perhaps make out a slight difference in the favour of methylthio-uracil. The material is all too small, however, to say anything definite about this point. But, the difference in the effect that I had expected to find — according to the results of the experimental

biological investigations was by no means encountered. On the whole, the two remedies had the same effect.

In patients with thyrotoxicosis the time for the thio-uracil effect appears to vary considerably and to depend on several factors.

The effect manifests itself rapidly in patients with primary, previously untreated, thyrotoxicosis without any complicating heart lesions. Altogether 20 patients belonging to this category have been treated — 4 with thio-uracil, 16 with methylthio-uracil. In all these patients the effect of the treatment could be recognized with certainty after 14—25 days (on an average, 16 days). Whether the disease has lasted for a long or a short period seems to make no difference; nor does the age of the patient or the size of the goiter seem to play any particular role in this respect.

If the patients have been treated with iodine immediately before the institution of this treatment, the thio-uracil effect will usually be slower in its appearance. The same observation has been reported already by *Astwood*[16], *Bartels*[19], *Eaton*[42], *Himsworth*[78], *Jackson*[83], *McGavack et al.*[118], *Meulengracht & Schmith*[137], *Palmer*[152], *Rose & McConnel*[164], and *William*[200]. As also I have observed now and then, *Palmer*[152] emphasizes that, in spite of the increased metabolism, the complaints of these patients subside fairly rapidly, whereas — according to *Astwood*[16] — the duration of the treatment with iodine is significant to the appearance of the thio-uracil effect.

In the other groups the patients are too few to allow of any definite conclusion. But it is to be mentioned that 4 patients with recurrent thyrotoxicosis did not respond to the treatment until after 25—44 days. Still, one patient with recurrent thyrotoxicosis responded to the treatment with surprising rapidity even though iodine therapy had been given before. In 4 patients with secondary thyrotoxicosis a definite effect appeared after 20—60 days. A complicating heart lesion was found in 2 patients with primary, untreated, thyrotoxicosis; and here the thio-uracil effect appeared after 30 and 35 days' treatment respectively. The possible significance of a complicating heart lesion has been mentioned already (p. 154); whether what was said there may apply also to these two patients cannot be settled.

Several authors have reported how long it takes before the thiouracil effect becomes manifest. But, as mentioned before, the estimation of this juncture is difficult. So, as was to be expected indeed, the statements on this point vary considerably. Contributory causes of this variation may be found in the size of the dose, the character of the thyrotoxicosis and the treatment given the patient previously.

Rose & Mc Connell[164] state that confinement to bed in the beginning of the treatment will shorten the time for the effect to appear. *William*[200] says that it is generally agreed that the thyrotoxic symptoms subside simultaneously with a decrease in the metabolism and a gain in weight. *Meulengracht & Schmith*[137] who have treated 80 patients with methylthio-uracil, found in all of them a decrease in the metabolism that was more abrupt in the beginning and accompanied by considerable gain in weight. *McGavack et al.*[118] found a gain in weight in all the patients in whom the thyrotoxicosis was under full control.

If there be a latent period before the appearance of the thiouracil effect, according to *Astwood*[15, 16], it is short — and shorter for the appearance of objective and subjective improvement than for the decrease in the rate of metabolism.

In patients responding favorably to the treatment, *Jackson*[83] was generally able to demonstrate an improvement of the clinical features within a few days. He states that these changes are noticed by the patients before there is any decrease in the metabolism. *Mc Gavack et al.*[118] were able to see some improvement after 6—7 days' treatment, *Paschkis et al.*[153] after 5—10 days. *Frisk*[55] emphasizes that the average length of time for an objectively demonstrable improvement is 8.3 days; and he states that the values for the metabolism and pulse rate begin to fall after 5—20 days, usually 6—7 days.

In uncomplicated cases, *Westergaard*[199] found the effect of the treatment fully revealed after 8—14 days; and *Rose & McConnell*[164] were able to demonstrate a fall in the metabolism amounting to + 15 % within an average of 2 weeks.

Himsworth[78] calculated that on an average it takes 29 days before a distinct improvement may be established, and generally two weeks before any particular effect is noticeable. According

to *Rose & McConnell*[164] it takes 2 1/2 weeks before the patients feel distinctly better.

Several authors have given data on the time it takes before the thyrotoxic symptoms have subsided completely, and the metabolism has returned to a normal level; and some of them continue with the initial dose until this result is obtained. In the majority of the patients mentioned here, however, with a view to the possibility of the untoward effect, the dose has been lowered as soon as a definite effect was ascertained, so that an estimation of the time for complete recovery is of minor significance.

Himsworth[78] states that the maximal effect appears gradually after 4 weeks. According to *Paschkis et al.*[153] it takes 2—3 weeks to obtain complete disappearance of thyrotoxic manifestations and for return of the metabolism to a normal level. *Williams & Bissell*[203] found that it takes 3—7 weeks before the metabolism returns to normal, while *Frisk*[55] gives *2—9 weeks* (averaging 26 days). *Meulengracht & Schmith*[137] state that it takes 4—8 weeks, *Newman et al.*[146] 3—9 weeks. *Bartels*[19] arrived at the same result as the last-mentioned, and he states that it takes about 1 day for each per cent increase in the rate of metabolism.

According to *Meulengracht & Schmith*[137] it also takes 1—2 months' treatment before the ordinary nervous symptoms disappear completely.

As mentioned already, I have not found any decisive difference in the effect of this treatment in young and in elderly patients. The same has been reported by *Eaton*[42] whereas *Himsworth*[78] states that young patients with toxic symptoms generally respond to the treatment sooner than elderly patients. It is to be mentioned that *Eaton*[42] found no difference in the effect in men and women.

Severe cases of thyrotoxicosis appear rather to react more rapidly to the treatment than mild cases (*Williams & Bissell*[203]). In keeping with this, *Palmer*[152] found that the higher the initial metabolism the earlier and more dramatic is the effect of the treatment, and vice versa. My own experiences point in the same direction — though only in cases of primary, untreated, thyrotoxicosis.

William[200], *Eaton*[42] and *Astwood*[16] have all observed that pa-

tients with thyrotoxic adenoma respond to the treatment more slowly than patients with primary thyrotoxicosis. *Bartels*[19], however, found no difference in the effect of these two categories.

It has been mentioned that 4 of our patients who were admitted with recurrent thyrotoxicosis were slow in their response to the treatment. This is quite in keeping with *Eaton's*[42] report on 4 patients with relapse who all reacted to the treatment but slowly.

The following points are to be emphasized:

1. There appears to be no decisive difference in the effect of thio-uracil and methylthio-uracil in cases of thyrotoxicosis.

2. The point of time for the appearance of the thio-uracil effect is subject to wide variations. The effect appears most rapidly in primary, untreated, thyrotoxicosis, in which it often may be ascertained after one week and, as a rule, is sure to be established after about 2 weeks' treatment. The effect seems to appear more rapidly in the severe cases of thyrotoxicosis. In the primary form of this lesion the duration of illness prior to the treatment, the age of the patient and the size of the goiter are of no decisive significance. Preceding treatment with iodine delays the appearance of the thio-uracil effect, which also seems to be more slow in patients with secondary thyrotoxicosis or recurrence of the lesion.

3. Generally, a definite thio-uracil effect may be reckoned to appear in any form of thyrotoxicosis.

Chapter IV

THIO-URACIL THERAPY AND PREOPERATIVE TREATMENT WITH THIO-URACIL

Thio-uracil Therapy.

a. *Effect on the Thyrotoxic Symptoms.*

As shown in Part II, Chapter II, thio-uracil therapy shows a clinical effect in more than 90 % of all cases of thyrotoxicosis. The time it takes before this effect appears is highly variable, depending, among other factors, on the character of the thyrotoxicosis.

Above all, the state of thyrotoxicosis is due to an increase in the production of the specific hormone of the thyroid. The cause of this increased production is still unknown. With a suitable dosage of thio-uracil, however, it is practicable not only to lower the hormonal production to a normal level, but also to keep it at this level for a considerable length of time. The dose required for this — as well as the whole question about the dosage — will be dealt with separately in Chapter V.

The thio-uracil therapy in such cases must be individualized. It is possible and also desirable, it is true, to give some guiding principles — as, for instance, with regard to the dosage — but to a certain extent the treatment has to be individualized as is evident also from the preceding chapter.

For this reason, I do not consider it important to give any detailed account of how long the patients stayed in the hospital after the commencement of the thio-uracil treatment. Some patients may safely be discharged after a few weeks' treatment — perhaps even after one week — whereas others require hospital treatment for several months. As the thio-uracil therapy in thyrotoxicosis is quite new, we have considered it important to

watch the patients most carefully, on which account several of them have been kept under hospital treatment longer than absolutely necessary — and probably longer than the future patients. No doubt, ambulatory treatment of the patients may be practicable, especially the relatively mild cases, but also this requires a very thorough observation. In the present material, however, it seemed desirable not to employ this form of treatment.

After their discharge from the hospital the patients have returned regularly for control — but, naturally, this does not apply to the patients given operative treatment. At first all these patients were readmitted to the hospital for 1—2 days for the sake of reexamination, but subsequently it was considered sufficient to let the patients return for ambulatory control.

As a rule, the discharged patients have returned for reexamination every other week, sometimes more frequently. Later on, the interval between the reexaminations has been prolonged, in some cases up to 2 (or 3) months. But, in addition, all the patients have been instructed implicitly to apply to the hospital or to their private physician if their state of health might not be satisfactory.

Under the treatment given, the thyrotoxic symptoms subsided completely in a good many of the patients. The present patient material is not uniform, comprising primary as well as secondary forms of thyrotoxicosis, besides cases of recurrence as well as several patients (about 20 %) who had been treated with iodine. For this reason as well as because the number of patients here is rather limited, the material is not serviceable as a basis for an estimation of the rapidity and sequence with which the various thyrotoxic symptoms subside under the thio-uracil treatment. Nor does this question appear to be of particular interest, however, as the various forms of thyrotoxicosis (*e. g.*, the primary form) naturally will include both qualitative and quantitative variations as to the number and intensity of the symptoms. Moreover, many external conditions may highly influence the already unstable emotional habitus of the patients and thus their general condition.

Psychic and motor restlessness, which highly characterizes these patients, is one of the first symptoms to subside. Still, tremor may

persist for a rather long time. The vasomotor lability and the increased sweat secretion likewise, as a rule, subside rapidly. The patient becomes calm and is feeling well increasingly, even though in many patients the nervousness may be made out yet for a long time. Also tiredness appears to be one of the symptoms that disappears but very slowly. Further, it is to be mentioned that in some of the patients a diarrhea has persisted long after the appearance of a decided improvement of the general condition.

Largely, the *pulse rate* follows the decrease in metabolism and improvement of the general condition. This applies to a majority of the patients in the present material, even though it cannot be established as a fixed rule — just as the decrease in metabolism and the clinical improvements of the patient may not always run parallel.

In one patient the pulse rate fell far more rapidly than corresponding to the metabolic rate and the clinical condition — and in 2 patients more slowly. In 5—6 patients with a slight degree of thyrotoxicosis the pulse rate was not increased to any extent worth mention, and it remained quite unaffected by the treatment.

On the whole, however, under thio-uracil treatment the pulse curve will give some good information about the effect of this treatment. On the other hand, it will hardly be justified to draw any conclusion from the pulse rate found in patients returning for ambulatory control.

Only a few of the patients presented complicated *heart lesions* of a rather severe degree. In one patient in whom electrocardiography at the commencement of the treatment showed the presence of arrhythmia perpetua and auricular fibrillation, both phenomena disappeared after 12 days' treatment, and the heart action became regular, whereas in another patient with a history of protracted heart lesion (5 years) auricular fibrillation appeared after 5 months' treatment. As in these patients the cardiac affection most often is a result of their thyrotoxicosis, it is only natural — unless the heart symptoms have persisted very long — that it subsides more or less completely as the thyrotoxic state is abolished. A striking example of this is found in patient No. 4, whose case record is given on p. 197. Also in the other patients with a herat

lesion, as a rule, an improvement of this affection appeared at the same time as the thyrotoxic symptoms disappeared.

In several patients the greater part of the thyrotoxic manifestations will disappear under the continuous treatment. Several of the patients treated here have apparently become completely symptom-free. The patients declare that they are exceedingly happy for the treatment given them, as they feel perfectly well — far better than they have been feeling for many years — just as well as before their illness, and so on.

An attempt to estimate the point of time when the patients became symptom-free, I think, would be of minor importance, as so many extraneous factors may exert their influence on this point. When, for instance, some authors state that it takes but a few weeks of treatment for the thyrotoxic manifestations to subside completely and for the reestablisment of a normal rate of metabolism, this may hardly be correct.

One of the more essential and constant symptoms of thyrotoxicosis is the enlargement of the thyroid, and as long as the goiter persists — no matter whether it be palpable or not — it would hardly be quite justified to speak of absence of symptoms. The same applies, among other things, to exophthalmus (as to struma and exophthalmus, see below).

There can be no doubt, however, that in a rather large number of cases of thyrotoxicosis it is practicable within the period of treatment here employed to arrive at the result that the patient feels perfectly well and normal, being able to work physically as well as mentally to full extent. Still, it is to be pointed out that some of these patients have been found less capable of standing adversity or psychic traumas than they were before their illness.

In other patients, however, the therapeutic result is far from satisfactory, the thyrotoxic symptoms — in particular nervous symptoms and tiredness — subsiding very slowly. The condition of the patient may be very good periodically, but there may be recurrence of the symptoms. In such cases, perhaps, an improper dosage may be the cause of the unsatisfactory course of the case.

As it has not been possible with thio-uracil or methylthio-uracil

alone to cure even one of the patients in the present material, this question will not be discussed further here. The possibility of complete recovery from thyrotoxicosis through the treatment with these remedies will be mentioned later on.

Weight and Metabolism. — In all thyrotoxicotic patients where the thio-uracil treatment shows a distinct effect, the decrease in metabolism is accompanied by a gain in weight if the treatment is continued for a sufficient length of time. In a few patients the presence of obesity may make a gain in weight undesirable; but in such patients it probably will be possible to prevent the gain in weight by means of a suitable diet.

Under the continued treatment with thio-uracil or methylthio-uracil the principal task will be to keep the patient on such a dose 1) that the state of thyrotoxicosis is completely under control, 2) that the rate of metabolism as far as possible keeps within normal values (± 10 %), and 3) that the body weight does not increase to undesirably high values. In one of our patients (No. 50), in spite of a reducing diet, the weight increased under the continued treatment to such high values that it was found necessary to lower the dose of methylthio-uracil, and this resulted in an increase in the metabolism to values above the normal.

It is further to be mentioned that it is not always possible to adjust a definite maintenance dose and let the patient continue with this dose. The thyroid-hormone requirement of the organism is not constant but dependent, for one thing, on extraneous conditions, so that a dose which in one period is found to be adequate, in another period was proved too small or too large. In some patients we have tried discontinuance of thio-uracil or methylthio-uracil, but in all such cases — with the exception of one — this has led to recurrence of the thyrotoxic symptoms, so that the treatment had to be continued. These questions, which will be further discussed in the following chapter, are mentioned here merely in connection with the effect of the continuous thio-uracil treatment on the metabolism and body weight.

In altogether 47 out of the present 54 patients, as mentioned, a distinct effect was obtained with thio-uracil or methylthio-uracil.

Curves for the metabolism and weight in 24 of these cases are

presented in Fig. 37. Of these 24 patients 6 were treated with thio-uracil, 18 with methylthio-uracil. All these patients have been under treatment for at least 3 months. Several other patients might have been included in this graph too; but as they are mentioned elsewhere, they are omitted here. Fig. 37 is aimed merely at conveying the impression of how the metabolism and weight in general have behaved under the continuous treatment of the pa-

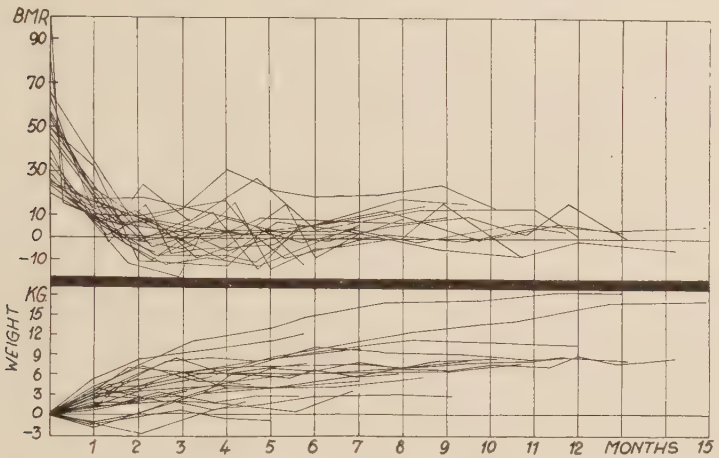


Fig. 37. Curves for the body weight and metabolism in 24 patients treated with thio-uracil and methylthio-uracil for at least 3 months.

tients. It is to be mentioned that these 24 patients include primary as well as secondary forms of thyrotoxicosis, besides a few cases of recurrent thyrotoxicosis and also patients treated with iodine prior to the thio-uracil therapy.

Only in the case of one patient who is not included in this graph (Patient No. 15, female, aged 61) though she had also been under treatment over 3 months, the values obtained for the metabolism were not in keeping with those here recorded. Besides thyrotoxicosis, this patient had also a complicating heart lesion. Under her treatment with methylthio-uracil the metabolism decreased from + 63 to + 28 in 5 weeks. At the same time, there was a distinct improvement of her clinical condition, whereas she had not yet commenced to gain in weight. The clinical improvement

persisted, and finally the weight began to increase, but the metabolism still kept at a level of about + 20 to + 30, now and then with an increase to + 40 or + 50.

When sometimes the rate of metabolism is rather high, this may be due, among other things, to the above-mentioned conditions together with efforts to lower the dose as far as possible — in order to lower the risk of untoward effects.

Goiter. — In thyrotoxicosis, as mentioned, the presence of a goiter is a very constant symptom, even though enlargement of the thyroid cannot always be ascertained positively. Naturally, the behavior of the goiter under continued thio-uracil treatment is a question of considerable interest even though it may be difficult at present to draw any indisputable conclusion from the findings in this respect. Still, a goiter that keeps increasing in size will in itself be an indication for operative treatment merely on account of its size. But, whether enlargement of the thyroid is to be looked upon as an unfavorable sign, and whether a diminution of its size is to be taken as a favorable sign, cannot yet be settled with certainty.

Often it is very difficult to estimate the size of the thyroid, and even more difficult to recognize minor variations in its size; here, even mere variations in the consistency of the goiter may be misleading. Under the continued thio-uracil treatment I have tried in the present patients to get some idea about the behavior of the goiter by means of fairly regular measurements of the circumference of the neck together with palpation of the goiter. These methods are to be looked upon as unreliable, however, and they may reveal only rather gross changes. Still as the size of the thyroid in normal persons too is subject to variation, albeit in a slight degree, it appears as if only the gross changes may be entitled to any particular interest. In estimating the size of the goiter, due regard has to be paid to the general gain in weight which, as mentioned before, may often be rather considerable.

Results. — Of the 54 treated patients 38 presented a noticeable goiter. In the remaining 16 patients it was not possible at any

time with certainty to demonstrate a goiter — neither before nor under the treatment.

In 38 patients the goiter was palpable. 10 of these patients were treated only with thio-uracil or methylthio-uracil through a rather short period (about 1 month) whereafter most of them were given operative treatment. In these 10 patients no change was observed in the size of the goiter.

Nor could any gross changes in the size of the goiter be demonstrated in 21 patients with a palpable goiter, who were all under treatment for a considerable length of time.

On the other hand, *in 7 patients the goiter increased considerably in size under the treatment.*

During the treatment, one of these 7 patients showed suddenly an increasing swelling and tenderness of the thyroid, which was enlarged beforehand; and at the same time the temperature rose to about 39°. After 2 weeks the temperature returned to normal, and the tenderness subsided, but the size of the goiter increased further though without giving any symptoms of compression. In 2 patients the size of the goiter increased quite considerably in connection with overdosage of the remedy. In one of these patients the metabolism decreased to — 12 — — 20 %, in the other to — 38 %; the latter patient will be mentioned further in Chapter V (Figs. 57 and 58), where the question of overdosage will be discussed too. The increase in the size of the goiter in these two patients is analogous to the goiter formation in a normal rat treated with thio-uracil. Of the remaining 4 patients 3 were submitted to thyroidectomy, among other reasons, because of the increasing goiter. In none of these 4 patients was the outcome of the thio-uracil treatment satisfactory and 3 of them showed also relatively slight untoward effects from the treatment.

No pronounced diminution in the size of the goiter was obtained in any of the patients.

Exophthalmus. — Among the 54 treated patients 21 showed more or less basedowian eye symptoms, but only 9 of these presented a definite exophthalmus. Among the basedowian eye symptoms, interest was taken only in exophthalmus.

Of the 9 patients with exophthalmus, 3 were submitted to thyroidectomy after 20—25 days of thio-uracil treatment; and in this period there was no change in the degree of exophthalmus. In 1 patient, with slight exophthalmus, this symptom persisted fairly unchanged after 6 months' treatment. In 5 patients the exophthalmus subsided markedly or completely under the treatment.

Effect on other Aspects of the Organism (Laboratory Tests).

In the course of the treatment with thio-uracil or methylthio-uracil, at certain intervals, various laboratory tests were made on the patients in order, if possible, to disclose any untoward effects from the treatment.

These tests were made not only while the patients were hospitalized, but also when they returned for reexamination, even though they were not carried out in every case. The extent to which these tests were performed will be evident from the following. Blood examinations were carried out on all the patients because at the time when this treatment was introduced here the literature had already brought some case reports where the treatment had been followed by a very injurious and dangerous effect on the bone marrow.

These examinations are to be considered in connection with the experimental studies on rats (Part I, Chapter VII).

As the untoward effects from the thio-uracil treatment will be dealt with separately (Chapter VI), no detailed mention of them will be made here.

Results.

Urine. — In all 54 patients the urine was examined fairly regularly for the presence of albumin in order to disclose a possibly noxious effect from the treatment on the kidneys.

Albuminuria was never encountered under the treatment with thio-uracil or methylthio-uracil.

Blood Urea. — Determinations of the blood urea concentration were performed on altogether 44 patients. The results are recorded graphically in Figs. 38 and 39.

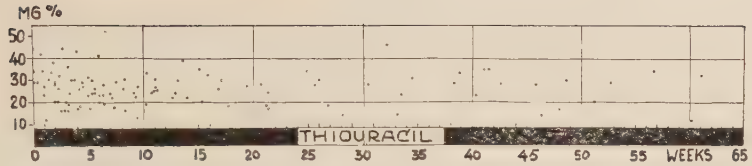


Fig. 38. Determinations of blood urea in 12 patients under treatment with thio-uracil.

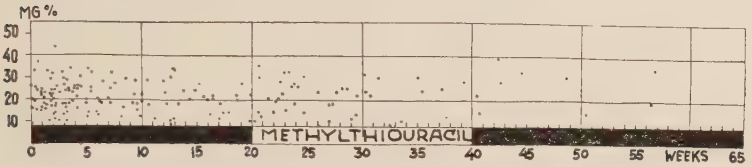


Fig. 39. Determinations of blood urea in 32 patients under treatment with methylthio-uracil.

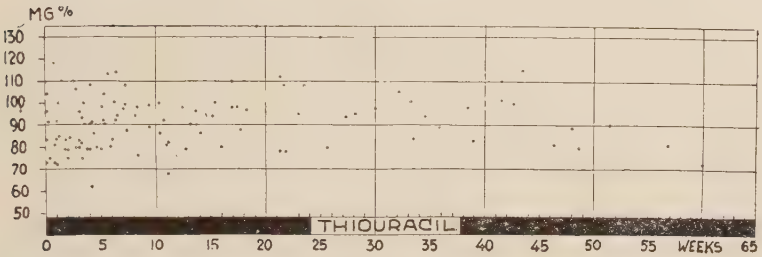


Fig. 40. Blood sugar determinations (fasting) on 12 patients under treatment with thio-uracil.

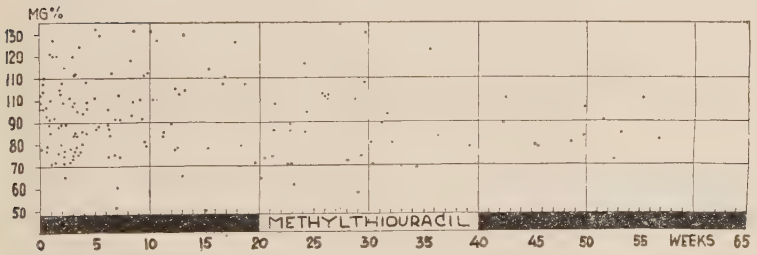


Fig. 41. Blood sugar determinations (fasting) on 28 patients under treatment with methylthio-uracil.

Abnormal values for blood urea were never obtained under the treatment with thio-uracil or methylthio-uracil.

Blood Sugar. — Blood sugar determinations (fasting) were carried out on altogether 40 patients. The results are recorded in Figs. 40 and 41.

Abnormal values for the blood sugar concentration were never observed under the treatment with thio-uracil or methylthio-uracil.

Sedimentation Rate. — Repeated determinations of the sedimentation rate were performed on altogether 41 patients, 10 of whom were treated with thio-uracil, 31 with methylthio-uracil. The largest number of such tests performed on one patient was 15. In additional 9 patients a single determination was performed.

Under the treatment with thio-uracil or methylthio-uracil, abnormal values for the sedimentation rate were observed only in cases where other causes *(e. g.,* infection) offered an adequate explanation of the increased values.

Hemoglobin Percentage. — Repeated determinations of the hemoglobin percentage were performed on altogether 47 patients, 12 of whom were treated with thio-uracil, 35 with methylthio-uracil. The greatest number of such determinations performed on one patient was 21.

Abnormal and otherwise unexplainable variations of the hemoglobin percentage were never observed under the treatment with thio-uracil or methylthio-uracil. No marked fall was ever observed. In patients showing low initial values the percentage often rose to a normal level. At the same time, red blood counts were made repeatedly on 5 patients without showing any abnormal variation.

Thrombocytes. — Platelet counts were performed on altogether 51 patients, 12 of whom were treated with thio-uracil, 39 with methylthio-uracil. The results are shown in Figs. 42 and 43.

In 3 patients treated with thio-uracil or methylthio-uracil the

platelet count has been less than 100000 (Fig. 42: 70000; Fig. 43: 77000 and 93000). In all 3 patients the values rose to a normal level under the continued treatment. At the same time the white blood count was normal in these 3 patients. In one case (Fig. 43) the platelet count fell to 100000 in the course of 30 days' treatment; as at the same time there was a fall in the white blood count (to 3080), and the patient became nauseated, thyroidectomy was performed 4 days later.

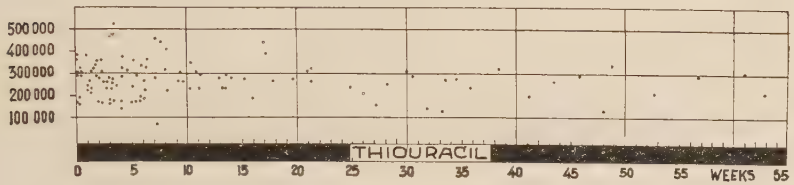


Fig. 42. Platelet counts in 12 patients under treatment with thio-uracil.

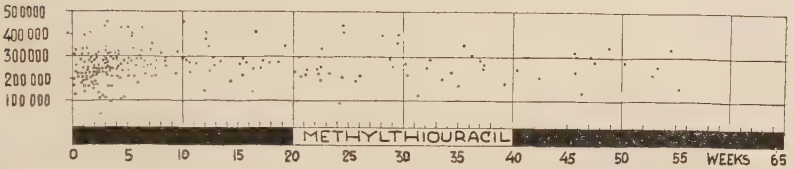


Fig. 43. Platelet counts in 39 patients under treatment with methylthio-uracil.

Otherwise, as a rule, any fall in the platelet count was followed by a rise, and clinical signs of thrombopenia have not been observed in any of the patients treated here.

White Blood Cells. — White blood counts were performed on altogether 53 patients, 12 of whom were treated with thio-uracil, 41 with methylthio-uracil. The findings are evident from Figs. 44 and 45.

In 19 of these 53 patients, under the treatment with thio-uracil or methylthio-uracil, there was a fall in the white blood count to less than 4000. In 14 patients this fall took place within the first month of treatment, and in 7 of these patients there was again a fall to less than 4000 later on, in the course of the treatment, sometimes after several months. Only in one case was this decrease in white blood cells (under 4000) accompanied by a con-

siderable fall in the platelet count and other untoward effects. This patient was then given operative treatment. In all the other patients the decrease in white blood cells was regularly followed by a rise to normal values under the continued treatment.

Differential counts were performed on altogether 28 patients, 12 of whom were treated with thio-uracil, 16 with methylthio-uracil.

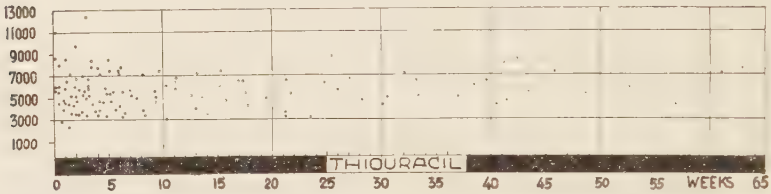


Fig. 44. White blood counts in 12 patients under treatment with thio uracil.

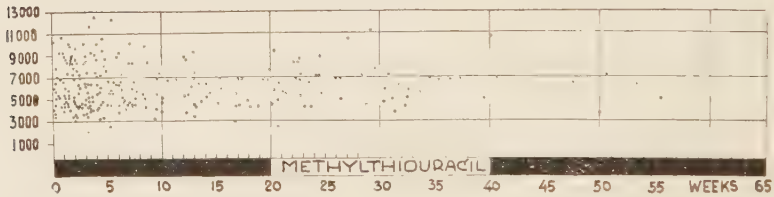


Fig. 45. White blood counts in 41 patients under treatment with methylthio-uracil.

The greatest number of such counts performed on one patient was 23. A differential count should be performed every time the white blood count falls below 4000, but this has not been done in the present material. Among the above-mentioned 19 patients in whom the white blood count fell below 4000, differential counts were made only on 12. In 7 of these 12 patients the lymphocytes were predominant, with a fall in granulocytes to a minimum of 36 %.

Among the patients in whom the white blood count never was found to be under 4000, the granulocyte count was never under 1500. On the other hand, in 3 patients with a fall in the white blood count to less than 4000, the minimum granulocyte count was respectively 1400, 1250 and 1000, but never under 1000. Relative

lymphocytosis was observed very often in these patients, but whenever the granulocyte count fell to low values, this fall was always followed by a rise. In the patient showing the lowest granulocyte count (1000) it rose again without any change being made in the given dose (0.8 g methylthio-uracil daily).

Clinical signs of agranulocytosis were never observed in any of the patients.

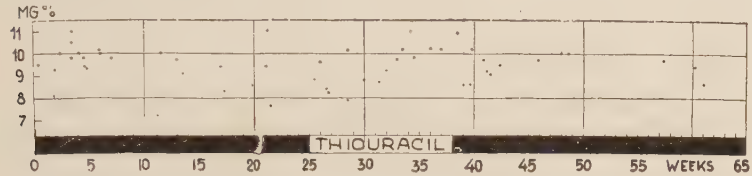


Fig. 46. Serum calcium values in 11 patients under treatment with thio-uracil.

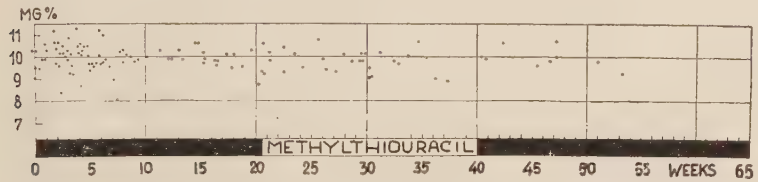


Fig. 47. Serum calcium values in 29 patients under treatment with methylthio-uracil.

Bone Marrow. — In 9 patients, 6 of whom were treated with thio-uracil, 3 with methylthio-uracil, the sternal bone marrow was examined after 1—2 months' treatment. The findings in these cases were rather uniform: lively activity in the erythrocytic or myelocytic system, or in both, but no other deviations from the normal.

Serum Calcium. — Determinations of serum calcium were performed on altogether 40 patients, 11 of whom were treated with thio-uracil, 29 with methylthio-uracil. The results are recorded in Figs. 46 and 47.

In 7 of the patients treated with thio-uracil the values of serum calcium were under 9.5 mg%; in 5 patients the values were under 8.5 mg% and in 1 patient the value was as low as 7.2 mg%. In 9 of the patients treated with methylthio-uracil the values were

under 9.5 mg%; in 3 they were under 8.5 mg%, and no value under 8 mg% was obtained in any of these patients.

No clinical signs of hypocalcemia were observed in the patients. As a rule, the very low values were followed by a rise — though not always to normal values.

Serum Cholesterol. — Determinations of serum cholesterol*) were carried out in 33 patients, 7 of whom were treated with

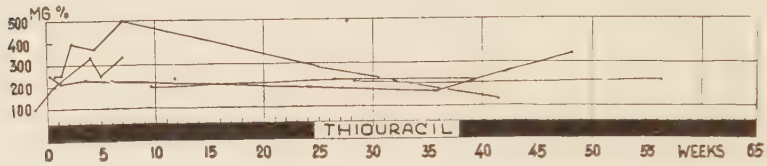


Fig. 48. Serum cholesterol values in 7 patients under treatment with thio-uracil.

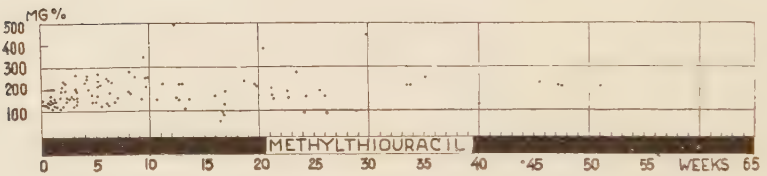


Fig. 49. Serum cholesterol values in 26 patients under treatment with methylthio-uracil.

thio-uracil, 26 with methylthio-uracil. The results are recorded in Figs. 48 and 49.

In 3 of the patients treated with thio-uracil the serum cholesterol values rose to a level over 300 mg%, but a value over 400 mg% was obtained only in one case. Among the patients treated with methylthio-uracil, values over 300 mg% were likewise found in 3 patients, in 2 of whom the values rose respectively to 493 mg% and 446 mg%. In the other patients the serum cholesterol values kept within normal limits — apart from a few low values.

Discussion.

In the treatment of all forms of thyrotoxicosis with thio-uracil or methylthio-uracil, the thio-uracil effect appears very regularly,

*) Obligingly performed by Dr. Mogens Faber.

and as a rule it can be recognized distinctly after 2—6 weeks' treatment. On continuation of the treatment a good many of these patients may become symptom-free and remain so through several months. This observation has been made by numerous other investigators — *e. g., Astwood*[16], *Donald & Dunlop*[39], *Eaton*[42], *Frisk*[55], *Gargill & Lesses*[59], *Himsworth*[78], *Jackson*[83], *McGavack et al.*[118], *Meulengracht & Schmith*[137], *Nussey*[148], *Palmer*[152], *Paschkis et al.*[153], *Rose & McConnell*[164], *Westergaard*[199], and *William*[200].

As in the present patient material, the therapeutic results reported by the above-mentioned authors appear chiefly to have consisted in *disappearance of complaints.* The patients feel well and are often able to resume their normal daily life to full extent. Frequently, however, the goiter will persist, and the thyroid may continue to be the site of marked histologic hyperplasia. If the treatment is discontinued, the symptoms will often return. Further, of course, the patients are not free from objective signs as long as they have a palpable goiter presenting histologically active features. Moreover, as already mentioned, a very critical estimation of the patients will in some cases reveal that the absence of complaints is merely apparent.

The dosage of the remedy has not been mentioned yet, as this question will be dealt with separately. Still, it is to be emphasized here that undoubtedly too low a dosage often is the reason why the state of the patient is not satisfactory. It is very important, however, to keep the maintenance dose as low as possible at all because of the risk of overdosage and untoward effects that naturally will increase with increasing dosage. Besides, the weight of the patient has to be taken into consideration too, as sometimes there is a tendency to gain in weight up to undesirably high values.

In patients kept on a certain maintenance dose it happens not infrequently that both the metabolism and the general condition of the patient may vary noticeably. This has to be looked upon as signifying variations in the requirement of thyroid hormone on the part of the organism; and it may explain why a patient who has been feeling perfectly well on a certain low dose suddenly may present slight symptoms of thyrotoxicosis together with increased

metabolism. Or, as seen in the case of patient No. 52 (p. 224), there may be a marked decrease in the rate of metabolism, accompanied by symptoms of beginning myxedema.

The aim must be to keep the patient on a dose that is not too small nor likely to lead on to overdosage. So, until the thio-uracil therapy has been worked out more thoroughly, it will be advisable not to let the intervals between the control examinations become too long.

When in some of the present cases this interval has been up to 3 months, it undoubtedly is to be looked upon as being too long. Still, as emphasized by *Meulengracht & Schmith*[137], at this juncture of the treatment the patient's own estimation of his condition may be taken as a criterion.

Whether the thio-uracil treatment has any curative effect, cannot be settled yet. *Himsworth*[77] states that recovery possibly may take place through atrophy of the thyroid following the preceding protracted hyperplasia. The same possibility is mentioned by *Rose & Mc Connell*[164] who think that the chronic hyperplasia of the thyroid possibly may lead to fibrosis and then to atrophy of this organ, perhaps also to cancer. Experimentally *Bielschowsky*[21] has been able to show that thio-urea injected together with a carcinogenic substance (2-acetaminofluorene) could produce malignant tumors in the thyroid, and that this did not take place when only one of these substances was employed. It is to be emphasized, however, that in one of our patients (see p. 197), on whom thyroidectomy was performed after 279 days of thio-uracil treatment, the thyroid was the site of maximal histological activity, without any sign of atrophy. At the same time, however, it is to be pointed out that in rats which had been under constant thio-uracil treatment from their 12' day of life to the 215' day the thyroid showed a slight increase in the interfollicular connective tissue.

Jackson[83] states that an eventual curative effect may be expected only in cases of primary thyrotoxicosis, as multiple toxic adenomas will not be removed by this treatment. *Astwood*[15] emphasizes that certain cases of thyrotoxicosis may require treatment for months or even years, whereas in other patients the thyrotoxic state is temporary and limited in itself. In such patients it should

be possible to maintain normal conditions in the organism during this limited period of illness.

In some of our patients we have tried discontinuance of the thio-uracil therapy, but even after one year of treatment the symptoms have returned. Only in one patient, in whom a slight degree of thyrotoxicosis had been present for 2 months, has the metabolism remained normal — at this writing for 3 months — after discontinuance of thio-uracil treatment which had been given only for 2 months. When such a favorable result has not been observed in other patients, it is possibly because we have been hesitant in trying discontinuance of the treatment in patients who for a considerable length of time have been symptom-free by means of a low maintenance dose. In reports by various authors — *e. g., Astwood*[16], *Eaton*[42], *Meulengracht & Schmith*[137], *Palmer*[152], *Rose & McConnell*[164] — it is stated, however, that, after thio-uracil treatment for a varying number of months, several patients have been symptom-free for up to 9 months after the discontinuance of the treatment.

In all the 9 patients reported by *Palmer*[152] the thyroid was of a diffuse hyperplastic type.

In these patients, according to *Astwood*[16], a change must have taken place in the endocrine system, but nothing may be said as to the character of this change as long as the pathological conditions that elicit the thyrotoxicosis are unknown. *Astwood*[16] emphasizes — and he illustrates his view with some examples — that changes in the size and, especially, the vascularization of the thyroid, may be of prognostic significance in this respect; if the signs of increased vascularization subside rapidly, there is a possibility of a remission proper.

The sequence in which the individual symptoms subside under the thio-uracil treatment appears not to be of particular interest. Indeed, the literature available to me has not given much information in this respect. Sometimes the results have been rather divergent, but this may be due in part to direct incomparability of the patient materials, partly to the many extraneous factors that may assert themselves.

As mentioned above in our patients the psychic and motor restlessness was one of the first symptoms to subside. The same applies to the vasomotor lability and the increased sweat secretion, whereas the nervousness often can be ascertained for a very long time.

Among the first symptoms to disappear, *Astwood*[16] emphasizes the irritability and anxiety, while *Himsworth*[78] mentions "skin flush". *Bartels*[18] says that the patients were able to notice a decrease in their nervousness as early as after 7—10 days of treatment. According to *Meulengracht & Schmith*[137], however, it takes 1—2 months before the general nervousness disappears. Diarrhea persists for a long time; and *Astwood*[16] states that it lasts longer than the increase in metabolism. Tiredness appears to subside very slowly. Still, *Bartels*[18] states that after treatment for about one week, the patients were able to notice an increase in muscular power, whereas *Astwood*[16] found muscular weakness to be the last symptoms to disappear.

A decrease in the *pulse rate* under the treatment is a common phenomenon that has been mentioned by several authors — *e. g.*, *Astwood*[16], *Bartels*[18], *Frisk*[55], *Jackson*[83], *Himsworth*[78], *Meulengracht & Schmith*[137], *Sloan & Shorr*[176].

Like *Bartels*[18], also *Meulengracht & Schmith*[137] state that palpitation and tachycardia subsided rapidly, and they further mention that no new characteristic symptoms appeared under the treatment. *Himsworth*[78] states more precisely that it takes about 2 weeks' treatment before the character of the pulse undergoes any change, and he emphasizes that a rapid pulse is the last symptom to subside. *Astwood*[16] found the pulse rate to be a valuable index of the state of the patients.

In the preceding, mention has been made of one of our patients in whom auricular fibrillation subsided after treatment for a rather short time. Similar observations have been made by *Meulengracht & Schmith*[137], *William*[200] and *McGavack et al.*[118]. Thus the last-mentioned authors emphasize that among 26 patients 7 had paroxysmal auricular fibrillation, which in all the patients subsided rather dramatically as soon as the metabolism returned to a normal level — and without the employment of digitalis.

The minute volume of the blood before and after thio-uracil treatment has been determined by *Rose & McConnell*[164], who were able to show that in 8 patients it was reduced simultaneously with the decrease in metabolism.

Exophthalmus.

In his review of the treatment of exophthalmic goiter, *Redisch*[158] (1934) states that severe degrees of exophthalmus constitute the symptom which is most difficult to abolish, and that it often may persist after the disease has been cured.

In the present material only 9 patients showed a distinct exophthalmus, and 3 of them were operated on after 20—25 days' thio-uracil treatment — without any change in the degree of exophthalmus. In 1 patient the exophthalmus persisted unchanged after 6 months' treatment. In the remaining 5 patients, on the other hand, the exophthalmus decreased or disappeared under the continuous treatment.

Similar observations are reported by *Astwood*[16] who states that the degree of exophthalmus nearly always appears to decrease within the first months of treatment. Also *Jackson*[83] as well as *Meulengracht & Schmith*[137] have observed the exophthalmus to subside under the treatment. The last-mentioned authors state that a slight degree of exopthalmus disappears within 1—2 months, while it might take a little longer for the more severe degrees to subside; but even in 3 patients with very pronounced exophthalmus this symptom disappears after 3, 4 and 6 months' treatment respectively.

In contrast hereto, *Eaton*[42] says that the exophthalmus remained unaffected by the thio-uracil treatment except in a few patients in whom a slight diminution could be made out. A similar result has been reported by *Himsworth*[78].

Aggravation of the exophthalmus has been observed by *Astwood*[16] in 1 patient, and also by *Williams & Bissell*[203]. The latter authors state that in their patient there was no improvement of the exophthalmus until the patient was given dried thyroid substance at the same time as thio-uracil.

Goiter.

Of the 54 patients dealt with here, 38 presented a distinctly noticeable goiter. As mentioned already, in 7 of these patients the goiter increased distinctly in size, whereas no gross changes could be demonstrated in the others.

It has been pointed out that it is very difficult to estimate the size of a goiter and, especially, variations in its size — something that has been emphasized also by *Astwood*[16], *Meulengracht & Schmith*[137] and *Paschkis et al.*[153]. *Astwood*[16] states that under thiouracil treatment the goiter generally becomes more soft and that this may be the reason why it seems to become smaller.

In 8 of his 9 patients with thyrotoxic adenoma, *William*[200] likewise noticed that the goiter became softer without any other particular change; in the 9' patient the goiter increased in size because of necrosis and hemorrhage in the thyroid from some unknown cause. In contrast to this, *Jackson*[83] says that under the treatment the goiter sometimes becomes smaller in size and more firm.

In order to attain a more accurate estimation of the size of the goiter under the treatment, *Meulengracht & Schmith*[137] adopted a figurative registration of its size, drawing the goiter on a schema. They employed this procedure in all their cases (a total of 80) and found the method quite serviceable. As the outcome of their investigation, they emphasize that in all their patients the goiter remains unchanged. This result is very interesting in view of the fact that, as mentioned above, in a good many of the same patients it was practicable to discontinue the treatment for several months — without recurrence of the thyrotoxic symptoms. Biopsy of the thyroid in these patients would have been very interesting with a view to a possible reduction in the histological activity of the gland.

In keeping with the results obtained by the writer, *Meulengracht & Schmith*[137] state that the goiter may increase a little in size and become a little more firm when the metabolism falls to subnormal values.

Astwood[16] found that during the first months of treatment the thyroid often increases in size though moderately, while a great

increase is a rare phenomenon. *Frisk*[55] likewise states that the thyroid increases in size after treatment for 2—3 months. Thus, among 16 patients treated merely for 3 months, the thyroid became larger in 11. *Frisk*[55] employed measurement of the circumference of the neck as criterion of this increase in size, stating that this increase was from 1 to 4 cm. Due allowance for the general increase in body weight, however, is an important point to be taken into consideration in this connection. *Frisk*[55] further claims that the enlargement of the goiter, which subsides again under the continued treatment, is in keeping with the enlargement of the thyroid in the experimental animals — an assertion that hardly may hold true unless the metabolism has decreased to subnormal values. *Palmer*[152], too, has observed some enlargement of the thyroid in the beginning of the thio-uracil treatment; and he states that this increase in the size of the goiter may be prevented by simultaneous administration of thyroxin or dried thyroid substance. With this combined thio-uracil and thyroxin treatment of patients with thyrotoxicosis, *Palmer*[152] has seen some excellent results — with regard to other symptoms of the disease too. Among 32 patients treated by *Himsworth*[78] the size of the thyroid remained unchanged in 30, while it increased in 2 patients, who were given operative treatment on this account. In 31 patients *Donald & Dunlop*[39] found no significant changes in the size of the goiter. The same applies to *Paschkis et al.*[153] who among 31 patients observed a change in the size of the goiter only in one case, namely: diminution.

Eaton[42] who has treated 40 patients found the thyroid to be further enlarged in some of them, diminished in others; still, he states that the average circumference of the neck before the treatment was 32.4 cm, after the treatment 32.9 cm. Nor did *Newman et al.*[146] find any uniform changes in the goiter under the treatment. *Rose & McConnell*[164] have treated 36 patients, in whom the size of the goiter remained unchanged in 27, while it became larger in 5, and smaller in 4. A diminution in the size of the goiter has been observed especially by *McGavack et al.*[118], who have treated 21 patients. In 14 of these the goiter decreased — in one of these, however, only after a slight temporary increase — and in the

remaining 7 cases the size of the goiter kept unchanged under the treatment. It is to be emphasized that 5 of the patients in whom the goiter was diminished were suffering from thyrotoxic adenoma. Finally, it is to be mentioned that during the first 6 weeks of the thio-uracil treatment *Williams*[202] found no noticeable changes in the size or consistence of the thyroid; on the other hand, he states that after several months of treatment the thyroid often decreases considerably in size.

Thus, there is by no means any complete concordance between the observations reported by the various authors — nor was this to be expected. Still, from the findings cited above it seems justified to conclude that in thyrotoxicotic patients under treatment with thio-uracil or methylthio-uracil there is no pronounced tendency of the goiter to change in size within the first year. In several patients the goiter becomes a little larger during the first months of treatment. But a marked increase in the size of the goiter is a rare phenomenon, and the same applies to a diminution, which may be observed only after several months of treatment.

Laboratory Tests.

As mentioned, albuminuria was not observed under the thio-uracil treatment, and the blood urea concentration remained at a normal level. *Mc Gavack et al.*[118] and *Sloan & Schorr*[176] determined the creatine output with the urine in their patients under thio-uracil treatment and they state that the creatine content of the urine was reduced under the treatment, while the creatine tolerance increased. *Mc Gavack et al.*[118] further found the hippuric acid output to be normal under the treatment, while they state that the treatment had no effect on the serum protein concentration; nor were they able to demonstrate any sign of injury to the liver from the treatment. Here it will be appropriate to add that in our patients the sedimentation rate was never found to be increased, unless it could be explained in a plausible way.

McGavack et al.[118] as well as *Gargill & Lesses*[59], *Jackson*[83], *Kahn & Stock*[92] and *Paschkis et al.*[153] have observed the appearance of jaundice in some of their cases and they think that a toxic hepatitis may arise under the thio-uracil treatment, on which

account it seems required to determine the icterus index at least in the beginning of the treatment.

In the present material the blood sugar values have always proved normal under the thio-uracil treatment. This is in keeping with the findings of a normal glucose tolerance as reported by *McGavack et al.*[118] and *Sloan & Schorr*[176]. In a patient with thyrotoxicosis, who at the same time was suffering from diabetes mellitus of the adrenal type, *Williams, Bissell et al.*[204] observed a distinct reduction in the degree of glycosuria under the thio-uracil treatment.

Changes in the blood picture under thio-uracil treatment will not be discussed here, but in a subsequent chapter dealing with the untoward effects of the treatment (Chapter VI).

Serum calcium determinations were performed on altogether 40 of our patients under treatment with thio-uracil or methylthio-uracil. In no less than 16 of these patients the values obtained were under 9.5 mg% — a value that corresponds fairly well to the lower normal limit. In 8 of these 16 patients the values were found to be under 8.5 mg%. The low values were obtained relatively more often under treatment with thio-uracil.

These observations led on to determination of the serum calcium and serum phophorus on 50 rats, 40 of which had been treated with thio-uracil from their 12' day of life to their 205' day, and at the same time the hind legs of the animals were examined roentgenographically (cf. Part I, Chapter VII). But these examinations showed no pathological changes.

Sloan & Schorr[176] state that under the thio-uracil treatment the phosphorus-calcium balance gradually becomes more positive; and they claim that the improvement in the calcium balance chiefly is due to a decrease in the calcium output with the urine or feces. Also *McGavak et al.*[118] found that calcium retention was promoted under the treatment. In this connection, it is to be emphasized that in our patient material no clinical evidence of hypocalcemia was observed.

According to *McGavack et al.*[118] the sodium, potassium and chloride contents of the blood are quite unaffected by the thio-uracil treatment.

In our material the serum cholesterol concentration was determined on 33 patients under treatment with thio-uracil or methyl-thio-uracil. In 6 of these patients the serum cholesterol concentration rose under the treatment to values over 300 mg%, and in several of these patients the values decreased again. But these analyses are not so frequently comprehensive to allow of any definite conclusion concerning the relation between the serum cholesterol values and the metabolism.

According to *McGavack et al.*[118], the normal values for serum cholesterol are between 150 and 200 mg%, while *Frisk*[55] gives 150—250 mg% as a normal limit. *Brøchner-Mortensen & Eggert Møller*[26] who have investigated this question, emphasize, however, that the normal range is considerably greater; and they further state that generally there is no difference between the values obtained in women and men and that in the individual patient the values are rather constant throughout the day. On an average, the serum cholesterol values are somewhat lower in thyrotoxicotic patients than in normal persons, but generally the values obtained in the former are still within the normal limits. In the thyrotoxicotic patients (altogether 51) whom the last-mentioned authors examined themselves, there was no evident correlation between the rate of metabolism and the serum cholesterol values. On repeated examinations on altogether 49 patients, on the other hand, they found the serum cholesterol values in 65 % of the patients to increase under the iodine treatment of thyrotoxicosis, and, roughly, this increase is inversely proportional to the changes in the metabolism.

Under thio-uracil treatment of thyrotoxicosis *Sloan & Schorr*[176] found a rise in the serum cholesterol concentration to the level of myxedema. *McGavack et al.*[118] have observed a striking tendency of these values to rise simultaneously with a decrease in the metabolism, resulting in clinical improvement; and they state that the variations in the values for serum cholesterol were opposite to the variations in the metabolism. *William*[202] was unable to confirm this observation because, he thinks, all his patients were suffering from thyrotoxic adenoma; and he emphasizes that in such patients the ratio between the values for the metabolism and for serum

cholesterol does not vary in the same way as in toxic diffuse goiter. Also *Frisk*[55] found a rise in serum cholesterol to normal values, parallel with the improvement in the thyrotoxic state of the patients. Under the continued treatment he found in some cases the same cholesterol values to rise above the normal limit; and he states that this happened especially to patients being treated with thio-urea. Under treatment with thio-uracil or methylthio-uracil he found only in 4 patients a slight and transitory rise in the values to a maximum of 306 mg%.

Palmer[152] states that under thio-uracil treatment the serum cholesterol values are of no particular significance as to the degree of thyrotoxicosis.

Preoperative Thio-uracil Treatment in Thyrotoxicosis.

Of the 54 patients mentioned in the preceding chapters who were treated with thio-uracil or methylthio-uracil, altogether 19 were subsequently given operative treatment. As the effect of thio-uracil treatment on the thyrotoxic state of these patients already has been mentioned too, this question will merely be touched upon here. As all the findings so far indicate that thio-uracil and methylthio-uracil exert their action in precisely the same way, and that any possible difference in the effect of the two substances is merely a difference in degree as to the intensity of the antithyroid effect, no particular distinction will be made in this chapter between the two remedies. For the sake of completeness, however, it is just to be mentioned that 4 of the operated patients were treated with thio-uracil, 15 with methylthio-uracil.

As the number of operated patients is rather small, the material does not allow of any far-reaching conclusion. On the correlation with the findings reported in the literature, the present results may give some valuable information about the effectivity of thio-uracil treatment as a preoperative therapeutic measure in thyrotoxicosis.

The purpose of the following investigations was to look into the operative and postoperative course of the cases after thio-uracil treatment — in particular, the effect of this treatment on the histological features of the hyperactive thyroid, besides the influence of iodine under preoperative thio-uracil treatment.

The age and sex distribution of the 19 operated patients is:

16 women, 25—68 years old
3 men, 40—63 years old.

Of these operated patients 18 were suffering from primary thyrotoxicosis, which in 8 of them had developed within the last 6 months. In 4, this lesion had persisted over 1 year; in 2 the duration of illness could not be estimated.

1 patient had secondary thyrotoxicosis of about 2 months' duration, after the persistence of a large goiter for 10 years (this case will be mentioned separately).

Of the 19 patients 9 had been given thio-uracil with a view to subsequent operative treatment — among other reasons, because they wished to be operated. In 7 of these cases a preceding iodine therapy had not given the result desired. These 9 patients were operated on respectively after 19, 26, 26, 35, 36, 37, 52, 64 and 76 days of thio-uracil treatment.

9 patients were operated on because the thio-uracil treatment gave no satisfactory result. In 5 of these cases relatively slight untoward effects appeared under the treatment. In 2 cases a considerable increase in the size of the goiter contributed to the decision on operative treatment. These 9 patients were operated on respectively 30, 32, 42, 67, 94, 119, 155, 247 and 292 days after the commencement of the thio-uracil treatment. In contrast to the first mentioned 9 cases, however, in the latter 9 the thio-uracil treatment was not continued in every instance until the day of the operation — among other reasons, because of untoward effects.

In one case the thio-uracil treatment gave a most favorable result, and yet it was decided to perform thyroidectomy after 279 days of treatment.

Treatment and Results.

I. *Thio-uracil and Methylthio-uracil as the Only Preoperative Remedies given:* 5 patients.

In 3 of these patients, who had not been given iodine beforehand (Nos. 8, 10 and 18) the thyrotoxic symptoms subsided under the

treatment but not completely. The weight began to increase and there was a pronounced decrease in the metabolism:

No. 8: + 83 → + 6 % (64 days)
No. 10: + 36 → + 12 % (16 days)
No. 18: + 50 → + 2 % (34 days).

Then thyroidectomy was performed. In all 3 patients the thyroid was richly vascularized and soft, and the parenchyma was red. The operative and postoperative course was quite uncomplicated, the operation being followed merely by a slight rise in temperature and pulse rate (maximal temperature 38.7°, maximal pulse rate 110).

In one patient (No. 29), who 3 weeks prior to the thio-uracil treatment had been given iodine for 1 month, the metabolism increased during the first week of treatment from + 71 % to + 81 %, and during the following 3 weeks it fell to + 47 %. At the institution of the treatment the thyrotoxicosis was very pronounced, but this condition improved noticeably. Still, the diarrhea persisted, and the body weight decreased gradually. Yet the operation was carried through after 36 days of thio-uracil treatment. The operative and postoperative course was uncomplicated except for a rise on the temperature (maximum 39.7°) and in the pulse rate (maximum 150) on the first 3 days after the operation.

A more detailed account will be given of the course of illness in the 5' patient (No. 4) as in this case the treatment gave an almost miraculous result and — as far as may be judged — saved the life of the patient.

Patient No. 4. Woman, 40 years old.

Past history of essentially good health.

The thyrotoxicosis commenced in July 1942 and was getting worse rapidly, on which account the patient was hospitalized in the same month. Protracted iodine therapy and sedatives did not improve her condition, and her metabolism rose from + 80 % to + 100 %. As a last resort, an attempt was made at thymectomy (no thymus was found) with the result that a violent thyrotoxic crisis set in.

X-ray treatment was tried, besides hormonal and vitamin therapy, but none of them gave any favorable result, and her condition remained so poor

that operative treatment could not be suggested. Gradually, under the violens thyrotoxicosis, the patient became extremely emaciated (see Fig. 51). The subcutaneous tissue became thickened and stiff as leather; contractures appeared in the hip and knee joints and the weight which on admission had been 55 kg, fell to 36 kg. There were intermediate periods of slight improvement, but at no time would it have been safe to perform an operation. The metabolism kept almost constant at a level between + 50 % and + 100 %. Gradually an extreme dilatation of the heart developed, besides auricular fibrillation, cardiac insufficiency with hydrothorax, swelling of the liver and edemas.

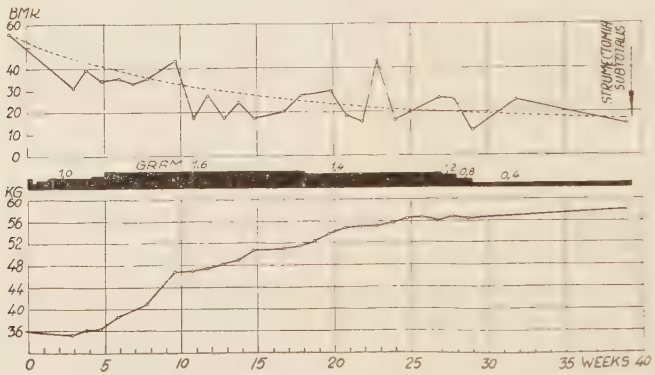
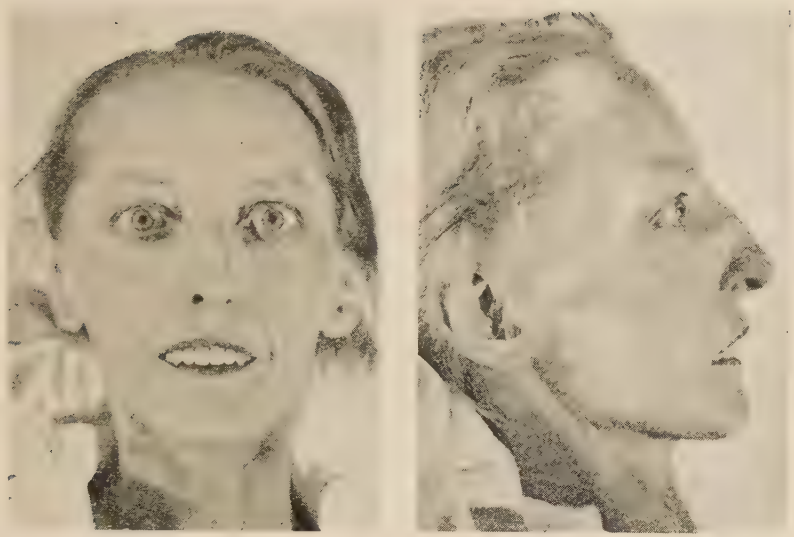


Fig. 50. Curves for dosage, body weight and metabolism in a woman, aged 40, with severe thyrotoxicosis, treated with thio-uracil (see the text).

In January 1944 the metabolism was between + 37 % and + 44 %, the lowest level so far. In this period the condition of the patient was better, but in February the metabolism increased again to a level about + 50 %.

On February 26, 1944, treatment with thio-uracil was commenced (see Fig. 50). In immediate connection herewith, the condition of the patient was aggravated considerably, and now she seemed rather moribund. Still, treatment was continued, and after about one week her condition commenced to improve. This improvement continued and led on to an almost miraculous change in the state of the patient: the thyrotoxic symptoms subsided, the very pronounced exophthalmus dissappeared to a large extent, the weight increased from 36 to 56 kg, and the metabolism showed a gradually decreasing tendency (see Fig. 50). The contractures were straightened out, and the patient got up on June 10, 1944, feeling very well and being able to walk about with the support of a cane.

Now the patient was discharged from the hospital, but 9 weeks later she was readmitted for the sake of operative treatment, because at that time we had but few experiences with thio-uracil treatment. Therefore in view of



1.

2.

Fig. 51. Woman, aged 40, with severe thyrotoxicosis, treated with thio-uracil.
1. After 19 months' treatment in hospital without any effect.
2. After additional 5½ months' treatment with thio-uracil.

the course of the disease in this case it did not seem justified to risk that an occasion favorable to operative treatment might be lost.

Subtotal thyroidectomy was performed 279 days after the commencement of the thio-uracil treatment. The thyroid was very large, strongly adherent to the surroundings, it was richly vascularized, soft and friable, and there was profuse bleeding from the gland.

The operation proceeded quite normally, and the postoperative course was entirely uncomplicated — the temperature did not rise over 38°, the pulse rate not over 76. The patient was discharged 2 weeks later, and she has been feeling well since. One year after the operation her only complaints were a little tiredness and slight functional dyspnea.

II. *Combined Thio-uracil and Iodine Treatment:* 14 patients.

a. In 2 patients who both had been treated with iodine for about 5 months, without any decisive effect on the state of thyrotoxicosis, *the iodine treatment was supplemented with methylthiouracil.* In one of the patients (No. 32) this resulted in a decrease in the metabolism from + 45 % to + 1 % (in 25 days), whereafter operation was performed. In the other patient (No. 22) the metabolism kept practically unchanged (about + 50 %) for 25 days. But, as the thyrotoxic symptoms had commenced to subside, and the body weight was increasing, operative treatment was decided on in spite of the high rate of metabolism. In both cases the operation was uneventful. The postoperative course was uncomplicated except for a brief rise in temperature to max. 39° and in the pulse rate to max. 136.

b. In 8 patients the *thio-uracil treatment was supplemented with iodine in the last week before the operation.* Of these patients, 4 had also been treated with iodine previously, without any decisive effect.

In 3 of these patients (Nos. 20, 31 and 23) the thyrotoxic symptoms subsided, and the metabolism decreased:

No. 20: + 77 → + 23 % (30 days)
No. 31: + 55 → + 14 % (35 days)
No. 23: + 52 → + 12 % (75 days).

Then the operation was performed.

3 patients (Nos. 34, 33 and 30) were treated with methylthiouracil respectively for 98, 155 and 244 days. Under this treatment

the metabolism became normal (after 22, 44 and 45 days, respectively), and it kept at a normal level under the continued treatment while the weight increased. The effect of the treatment on the nervous symptoms was not satisfactory, however — besides, in No. 30 there was also an increase in the size of the goiter — on which account an operation was performed. The operative and

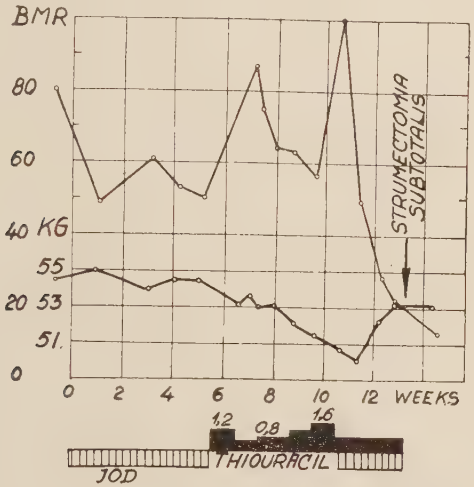


Fig. 52. Curves for dosage, body weight and metabolism in a man, aged 63, with severe thyrotoxicosis, treated with iodine and thio-uracil.

the postoperative course was entirely uncomplicated in all the 6 cases mentioned except for a brief rise in the temperature to max. 38.8 and in the pulse rate to max. 122. In 2 patients there was no postoperative increase in the pulse rate.

Particular mention is to be made of 2 other patients in this group:

Patient No. 3. Man, 63 years old.

Past history of essentially good health.

For about 10 years the patient has had a large goiter, which never inconvenienced him. During the last 2 months, increasing thyrotoxic complaints. 6 weeks of iodine treatment had no effect whatever on the rather pronounced thyrotoxic state of the patient, and the metabolism kept at a level of about + 55 %. Then the iodine therapy was discontinued, and on the same day thio-uracil treatment was commenced. This was followed by a violent, acute, aggravation of the condition of the patient with a marked

increase in the metabolism and fall in body weight (see Fig. 52): the patient became markedly thyrotoxicotic, poorly, tired and sweating, with diarrhea, and the heart action became irregular — of the perpetua type. As the metabolism decreased but slowly the thio-uracil dose was increased, and this resulted in an additional increase in the metabolism and aggravation of the general condition of the patient.

As now the thio-uracil dose was lowered, and iodine was given again, a complete change appeared in the condition of the patient: the metabolism decreased markedly, the body weight increased, and the thyrotoxic symptoms subsided.

Then the operation was performed, 52 days after the commencement of the thio-uracil treatment. The operative and postoperative course was uncomplicated — apart from a rise in temperature to max. 38.8°, and in pulse rate to 108.

Patient No. 17. Woman, 62 years old.

For many years the patient had been troubled with cardiac symptoms, especially palpitation and a sensation of precordial pressure. During the last 4 months before admission, functional dyspnea, increasing to orthopnea. Through the last 3 months, confinement to bed. For some length of time the patient had had rheumatic pains in various joints (progressive primary polyarthritis). The duration of the thyrotoxicosis could not be estimated with certainty. The appearance of the patient was strongly characterized by the thyrotoxic features.

Iodine therapy had been given for 49 days without any effect whatever, and hence thio-uracil treatment was now instituted while the iodine treatment was continued for 2 weeks more. During these 2 weeks the metabolism increased from about + 80 % to about + 100 %. 2 weeks after the discontinuance of the iodine treatment the metabolism had increased to + 123 %, though without the patient feeling any aggravation of her condition. Then the metabolism decreased gradually for one month to + 32 %, while the thyrotoxic symptoms subsided at the same time. Now operation was performed, without any complications. Postoperatively the temperature rose to a maximum of 38.8° and the pulse rate to 108. Two days later both the temperature and pulse were normal. There was some secretion from the operated wound which gradually went on to a suppurative inflammation. A few days after the operation, however, there was an acute exacerbation of the rheumatic infection, and the condition of the patient was complicated by bronchopneumonia. The patient died 24 days after the operation. Autopsy revealed no changes of particular interest.

c. In 4 cases (patients Nos. 26, 21, 54 and 19) the thio-uracil treatment was discontinued a short time before the operation, being replaced with iodine therapy. The treatment of 3 of these patients is recorded schematically in Table 36.

TABLE 36.

Thio-uracil Treatment replaced with Iodine Therapy shortly before the Operation.

Patient No.	Duration of treatment with thio-uracil	Preoperative iodine treatment	Remarks
26	30 days	11 days	Thio-uracil treatment without effect. Metabolism about + 35 %.
21	83 days	9 days	Unsatisfactory result from the thio-uracil treatment.
54	286 days periodical	5 days	Unsatisfactory result from the thio-uracil treatment.

In the case of patient No. 19 the treatment with methylthio-uracil was discontinued after 21 days because of its untoward effects. Iodine treatment was commenced 12 days later, and the patient was operated on after additional 9 days.

None of these patients had received iodine before. In the first 3 cases the thyrotoxicosis was light, while in the fourth case it was moderately severe. In all 4 cases the operative and postoperative course was uncomplicated exept for a rise in the temperature and pulse rate to max. 38.5° and 100, respectively.

Histological Findings.

The histological findings in the thyroid tissue removed from the above-mentioned 19 patients with thyrotoxicosis are recorded schematically in Table 37.

TABLE 37

Histological Findings in Thyroid Tissue resected from 19 Patients with Thyrotoxicosis, treated with Thio-uracil or Methylthio-uracil.

Patient No.	Treatment	Weight	Resected thyroid tissue. Histological findings
	I. *Thio-uracil or methylthio-uracil as the only remedy given:*		
8	Thio-uracil	18 g	Thyrotoxic goiter in active state. No lymphocytic infiltrations.

Patient No.	Treatment	Weight	Resected thyroid tissue Histological findings
10	Thio-uracil	31 g	Thyrotoxic goiter, showing marked activity. A single small lymphocytic infiltration observed.
18	Methylthio-uracil	45 g	Thyrotoxic goiter with signs of extreme activity. Lymphatic infiltrations very few and very small.
29	Methylthio-uracil	45 g	Thyrotoxic goiter with areas of activity and other areas stamped by iodine therapy. No lymphocytic infiltrations. (3 weeks prior to the institution of the treatment with methylthio-uracil the patient had been given iodine 1 month).
	II. *Combined thio-uracil and iodine therapy.*		
4	Thio-uracil	100 g	Thyrotoxic goiter, showing pronounced activity. No lymphocytic infiltrations.
32	Iodine + methyl-thio-uracil	30 g	Thyrotoxic goiter, showing evidence of iodine therapy, but still active. Few and small lymphocytic infiltrations (previous iodine therapy ineffective).
22	Iodine + methyl-thio-uracil	55 g	Thyrotoxic goiter, showing evidence of iodine therapy, but still active. No lymphocytic infiltrations (previous iodine therapy ineffective).
20	Methylthio-uracil + iodine preoperative	55 g	Thyrotoxic goiter in mostly quiescent colloid stage — evidence of iodine therapy. No lymphocytic infiltrations. (Previous iodine therapy ineffective).
31	Methylthio-uracil + iodine preoperative	33 g	Thyrotoxic goiter, with evidence of iodine therapy, but still active. No lymphocytic infiltrations.
23	Methylthio-uracil + iodine preoperative	68 g	Thyrotoxic goiter, showing marked activity, but with a few large follicles filled with colloid. No lymphocytic infiltrations. Previous iodine therapy ineffective.

Patient No.	Treatment	Weight	Resected thyroid tissue Histological findings
34	Methylthio-uracil + iodine preoperative	50 g	Thyrotoxic goiter, in mostly quiescent stage — evidence of iodine therapy. No lymphocytic infiltrations.
33	Methylthio-uracil + iodine preoperative	35 g	Thyrotoxic goiter, with evidence of iodine therapy, but still very active. No lymphocytic infiltrations.
30	Methylthio-uracil + iodine preoperative	80 g	Thyrotoxic goiter, with slight trace of iodine therapy and preponderantly great activity. Small scattered lymphocytic infiltrations. (Previous iodine therapy ineffective).
3	Thio-uracil + iodine preoperative	85 g	Thyrotoxic goiter, with some areas showing activity, other areas in a colloid quiescent stage. No lymphocytic infiltrations. (Previous iodine therapy ineffective).
17	Methylthio-uracil + iodine preoperative	40 g	Thyrotoxic goiter, showing evidence of iodine therapy, but still active. Small lymphocytic infiltrations. (Previous iodine therapy ineffective).
26	Methylthio-uracil — discontinued — iodine preoperative	30 g	Thyrotoxic goiter in quiescent colloid stage. Few small lymphocytic infiltrations.
21	Methylthio-uracil — discontinued — iodine preoperative	53 g	Thyrotoxic goiter, showing evidence of iodine therapy, but still active. Small lymphocytic infiltrations.
54	Methylthio-uracil — discontinued — iodine preoperative	23 g	Thyrotoxic goiter, partly nodular, showing evidence of iodine therapy. No lymphocytic infiltrations.
19	Methylthio-uracil — discontinued — iodine preoperative	60 g	Thyrotoxic goiter, nodular and colloid. No lymphocytic infiltrations.

Before entering into a discussion of the therapeutic results and their comparison with the results reported by other authors it will be appropriate briefly to mention the effect of iodine on the thyroid.

Effect of Iodine on the Thyroid in Thyrotoxicosis.

Means[135] states that the effect of iodine on the state of thyrotoxicosis is not due to any neutralization of, or change in, the thyroid hormone present nor to a change in the sensitiveness of the tissues to this hormone. On the contrary, the iodine effect involves the functional capacity of the thyroid, bringing the hyperplastic and highly active epithelial cells of the thyroid into a more passive phase. Thus, the output of thyroid hormone from the gland is lowered, and colloid is deposited in the follicles.

The thio-uracil effect on the thyroid is of a character quite different from that of the iodine effect. Somehow — in a way not fully elucidated yet — thio-uracil inhibits the formation of the thyroid hormone. Thus the hyperplastic epithelial cells of the thyroid are by no means brought into a quiescent state, as is often the case under the treatment with iodine. On the contrary, the increased activity of these cells persists, but as yet it has not been fully established which product results from the continued activity of the epithelial cells.

Means[135] emphasizes that the most adequate idea concerning the toxic goiter is that an unknown factor makes the thyroid evacuate its depot of colloid, forcing its epithelial cells to increased secretory activity. The administration of iodine by no means lowers the effect of this factor, but it brings about that mechanically or chemically — or perhaps in both ways — a barrier is raised that obstructs the delivery of the hormone to the organism. In the course of time this obstruction may be overcome, but as long as it exists the delivery of thyroid hormone to the organism will never attain the same magnitude as if this barrier was absent. A perfectly refractory state of the organism to iodine is conceivable only if the iodine has completely lost its ability to form the barrier mentioned. *Means*[135] states, however, that such a condition is not likely to occur.

Palmer[152] says that presumably thio-uracil tends to correct a disturbance in the endocrine equilibrium in a way deviating from the action of iodine. Among other things, this assumption is based upon the fact that an improvement of the general condition of the patient under treatment with thio-uracil usually precedes a de-

crease in the metabolism, or it is independent of variations of the metabolism. Furthermore, *Palmer*[152] also bases his view on the circumstance that the thio-uracil effect also appears in patients refractory to iodine.

Several things indicate that the thio-uracil treatment has no direct influence on the unknown factor which gives rise to the increased activity of the thyroid. Nor has iodine any direct effect in this respect. The latter is evident from studies reported by *Okkels*[149], in which the preoperative iodine therapy is shown not to have any effect on persisting hypertrophy of the Golgi apparatus; probably the cellular hyperactivity continues in undiminished degree, and it will be logical therefore to assume that the factor which induces this hypersecretion must be an extrathyroid principle. Apparently, however, it is an entirely different matter that iodine as well as thio-uracil seem to be able, each in its own way, indirectly to eliminate this factor by reestablishment of an endocrine equilibrium in the organism through a considerable length of time.

Not infrequently we meet with patients who fail to respond to the iodine therapy with the improvement of the thyrotoxic symptoms aimed at. When such iodine-treated patients are given thio-uracil treatment, as mentioned already, the effect usually appears more slowly. Presumably this is due to the possible circumstance that even though the iodine therapy in itself has been ineffective, it still has given rise to storage of thyroid hormone in the gland Now, thio-uracil has no effect on this finished hormonal product (cf. Part I, Chapter X), so that the effect of this remedy will manifest itself only as the store of hormone gradually is used up. Theoretically, as emphasized before, thio-uracil treatment through a sufficient length of time should always result in a thyroxin deficit in the organism. But, according to *Astwood*[16] the clinical dose of thio-uracil does not completely block the formation of thyroid hormone, and hence, it is easy to understand that sometimes this deficit is very slow in being realized.

The favorable influence of the iodine treatment upon the capacity of the thyroid for storage of colloid, however, may be utilized with advantage in the preoperative thio-uracil treatment

of patients with thyrotoxicosis. This question will further be discussed below.

Discussion.

The experiences with the 19 operated patients reported in this chapter indicate that both thio-uracil and methylthio-uracil are highly serviceable for preoperative treatment of patients with thyrotoxicosis. The same experiences have been reported, for instance, by *Alsted & Lindholm*[6], *Bartels*[18, 19], *Freiesleben et al.*[52], *Frisk*[55], *Jackson*[83], *Meulengracht & Schmith*[137], *Palmer*[152], *Paschkis et al.*[153], *Rawson, Evans, Means et al.*[155], *Rose & McConnell*[164], and *Westergaard*[199].

It has been emphasized before that the thio-uracil effect is most likely to appear in all forms of thyrotoxicosis provided that the treatment is carried through for a sufficient length of time. It has also been emphasized, however, that the therapeutic result is by no means always satisfactory. Moreover, it is still an unsettled question as to what extent the thio-uracil treatment may have a curative effect. Several patients under thio-uracil treatment request to be treated operatively — as they say, "in order to get over with it". In other cases, the operative treatment has to be looked upon as desirable for the following reasons: 1) the thio-uracil treatment may not have the effect desired, for instance, on the common nervous symptoms; 2) the goiter may increase in size and eventually give symptoms of compression; and 3) the appearance of other untoward effects may require discontinuance of the treatment. Relatively slight untoward effects need not always make it necessary to discontinue the treatment; if this is done anyhow it will often be possible to resume the treatment later on. Still, it is obvious that the risk of serious untoward effects is greater in these patients than in patients who have shown no sign of any such effect. In addition, *Palmer*[152] emphasizes that patients who are unable to return for control examination should be operated on. He further says that patients with a preexisting adenoma or colloid goiter that has become toxic should be given operative treatment, as no diminution in the size of the goiter can

be expected in such cases. Whether this assertion be correct may be decided only after a longer observation period.

The inhibitory effect of the thio-uracil treatment on the production of thyroid hormone will fairly rapidly assert itself with the initial doses here employed (about 0.8 g daily — cf. Chapter V). After 3—4 weeks' treatment the inhibition may be looked upon with certainty as established; probably this has taken place long before. As mentioned, *Astwood*[16] emphasizes that the clinical thio-uracil dose does not completely block the formation of the thyroid hormone. Yet, the capacity of the thyroid for sudden production of large amounts of thyroid hormone is bound to be greatly reduced. On the other hand, thio-uracil has no influence on the reserve stock of thyroid hormone present in the gland.

Under these theoretical considerations it has not been considered necessary to postpone the operation till the thyrotoxic symptoms have subsided, and the metabolism has returned to a normal level. Sometimes the operation has been performed in spite of increased metabolism, and in spite of the fact that the thyrotoxic symptoms just have commenced to subside. This was done, for instance, in Cases 22 and 29, in which the operative as well as the postoperative course was quite uncomplicated. In keeping with this, *Palmer*[152] plans the operation when the metabolism has decreased to $^1/_2$—$^1/_3$ of the initial value. He states that probably the physiological balance is obtained before this manifests itself in the metabolism, and hence he makes no effort to obtain a normal rate of metabolism before going on to the operative treatment. In contrast hereto, *Bartels*[19] claims that the thio-uracil treatment should be continued until the maximal effect is obtained, that is, till the metabolism has become normal or almost normal, and the thyrotoxic symptoms have subsided. *Bartels*[19] mentions two cases, and *Paschkis et al.*[153] and *Westergaard*[199] have each reported one case in which the operation, performed before the metabolism has become normal, gave an unsatisfactory result with a severe postoperative reaction, which in the case reported by *Paschkis et al.*[153] terminated fatally 24 hours after the operation. If, on the other hand, the metabolism has become normal and the thyrotoxic symptoms have subsided, according to *Bartels*[19] the operation may be

performed without any risk; and he emphasizes that the value of the thio-uracil treatment, among other things, lies in the reduction of the operative risk. Also *Jackson*[83] asserts that the most serious risk in the operative treatment of patients with thyrotoxicosis appears to be brought under control by means of thio-uracil. After several weeks' treatment with this substance there is a noticeable reduction in the postoperative reaction in primary as well as secondary thyrotoxicosis. In cases where previously the operation had to be performed in two seances, it now can be carried through in one. This is emphasized also by *Bartels*[19] who now removes even very large goiters in one seance.

Administration of iodine immediately before the thio-uracil treatment will usually, as mentioned, postpone the effect of the latter, probably on account of storage of thyroid hormone. In 2 of our iodine-treated patients (Nos. 3 and 4), however, another and more puzzling reaction was observed. In both cases the iodine treatment was discontinued simultaneously with the institution of the thio-uracil treatment, and this gave rise to an acute and quite considerable aggravation of the thyrotoxic condition. *Astwood*[16] has reported a quite analogous case. As aggravation of the thyrotoxic condition on discontinuance of the iodine treatment alone as a rule appears but gradually, and as the thio-uracil treatment in previously untreated cases — as far as we know — has never given rise to aggravation of the thyrotoxicosis, the cause of the aggravation in the cases here mentioned will have to be looked for in the interaction between these two conditions, without it being practicable at present to say anything definite about the matter.

On account of these observations, in our material the iodine treatment was continued after the thio-uracil treatment was instituted, and as a rule the employment of iodine was then discontinued 1—2 weeks later. An example of this is seen in Fig. 53.

In two patients (Nos. 22 and 32) the apparently ineffective iodine treatment was supplemented with methylthio-uracil, and both remedies were given until the operation which was performed after 25 days' thio-uracil treatment with fully satisfactory results.

The first 3 patients mentioned in this chapter (Nos. 8, 10 and 18) were treated before the operation with thio-uracil or methylthio-

uracil exclusively. Likewise, patient No. 4, was treated with thio-uracil alone for 279 days prior to the operation. In all these 4 patients the thyroid was found at the operation to be soft, very richly vascularized and rather troublesome to resect. This does not apply to patient No. 29, however, who had been treated with thio-uracil alone for 36 days but had been given iodine a few

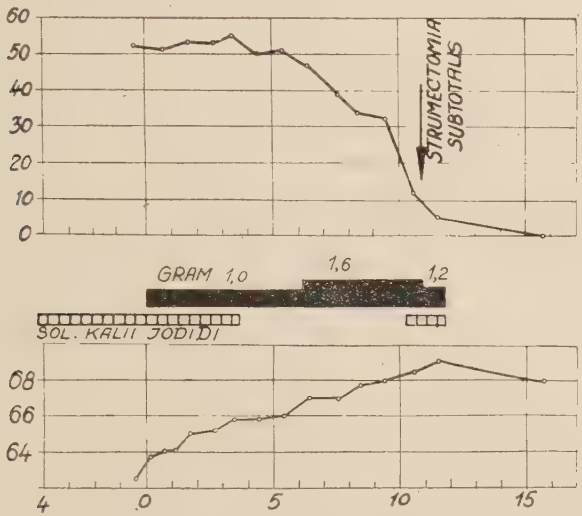


Fig. 53. Curves for dosage, body weight and metabolism in a man, aged 40, with rather severe thyrotoxicosis, treated with iodine and methylthio-uracil.

weeks before. That resection of the thyroid is disagreeable when beforehand the patient has been given thio-uracil treatment exclusively, is confirmed, among others by *Bartels*[18], *Freiesleben et al.*[52], *Jackson*[83], *Meulengracht & Schmith*[137], *and Westergaard*[199], whereas *Palmer*[152] claims that the thio-uracil treatment makes no difference in the hemorrhage, risk of embolism or prothrombin time; still, he recommends administration of vitamin K for 3 days before and after the operation.

Jackson[83] asserts that thio-uracil causes an increased vascularization of the thyroid or, at least, an increased tendency to hemorrhage.

Because of the technical difficulties in the operation after pre

operative treatment with thio-uracil exclusively, we have preferred to give the patients iodine for about one week prior to the operation. This results in storage of the colloid, so that the thyroid becomes more firm, and our experiences show that the hemorrhage then is reduced. Similar observations have been reported by *Bartels*[19] and *Jackson*[83].

In normal rats the thio-uracil treatment produces a marked hyperplasia of the thyroid parenchyma, with an increase in the weight of the gland. In the literature it has been emphasized repeatedly that this effect is not prevented by iodine, whereas it is completely absent when thyroxin is given simultaneously with thio-uracil.

In some experiments, reported in Part I, Chapter X, it was observed, however, that iodine or diiodotyrosine given to rats simultaneously with methylthio-uracil causes no particular reduction in the size of the goiter, whereas the histological features of the thyroid undergo a noticeable change, as, for one thing, the gland then contains far more colloid than if the animals are given methylthio-uracil alone.

These experimental findings correlated with the clinical experiences from the mentioned patients indicate that apparently the thio-uracil treatment has no influence on the capacity of the thyroid for storage of colloid.

Jackson[83] continues the thio-uracil treatment until 3 days after the operation, and then he continues giving iodine till the metabolism has become normal. In contrast hereto, *Bartels*[19] commences the iodine therapy 3 weeks before the operation and discontinues the thio-uracil treatment 1 week before the operation. In the present material we have tried discontinuance of the thio-uracil treatment before the operation or on the day of the operation and continuance of this treatment for 1—2 weeks after the operation — without noticing any difference in the effect. On the other hand, the patients who received iodine immediately before the operation were always given this remedy after the operation too, till the metabolism had become normal.

No particular mention will here be made of the operation itself

except that subtotal thyroidectomy was performed in one seance on all the 19 patients dealt with in this chapter.

In thyrotoxicosis, as mentioned, there is an accelerating factor which induces increased activity in the thyroid. This factor is still unknown. It seems obvious to think, however, that the thyrotropic principle from the anterior pituitary may play a rôle, for instance, in the relatively infrequent cases of climacteric thyrotoxicosis arising after the abolition of the inhibitory effect from estrin on the anterior pituitary lobe. The significance of thyrotropic principle in the majority of the cases of thyrotoxicosis has not been settled yet, and possibly a neurogenic factor may play some rôle here too. In this connection it is to be emphasized that *Sunder-Plassmann*[185] has been able to demonstrate that each epithelial cell in the thyroid follicles is supplied with a sympathetic neurofibril. He also sets up the concept of neurohumoral cells which — like a sort of wandering cells — may be found not only in the epithelial lining of the follicles but also in the interfollicular connective tissue. The same cells have been described also by *Altmann*[7], *Borell & Holmgren*[24] and *Severinghaus*[174].

When a thyrotoxicotic patient is being treated with thio-uracil, the accelerating factor of the thyroid may hardly be involved by the effect of this treatment. For this factor keeps up its action even after thio-uracil has made the thyrotoxic symptoms subside. If the administration of thio-uracil is stopped at this juncture, the symptoms return as strong as before.

If under the thio-uracil treatment the metabolism is forced down to subnormal values, something similar will happen as results from thio-uracil treatment of normal rats: the thyroid will be submitted to an increased action of the thyrotropic principle, and thus the goiter will increase further in size, while at the same time a state of hypothyroidism develops (see Fig. 58). It seems reasonable to assume — even though this has not been proved yet — that under these conditions the histological activity in the thyroid will increase at the same time.

According to the histological studies carried out in the present work, I find it justified to think that the thio-uracil treatment

otherwise does not directly alter the histological features of the thyroid in patients with thyrotoxicosis.

It is to be emphasized, however, that the lymphocytic infiltration found in the present histological material appears to be less pronounced than generally encountered in active goiters, which sometimes show rather extensive infiltration with lymphocytes.

In many respects, the histological picture of the thyroid seen after thio-uracil treatment is identical with the appearance of the untreated thyrotoxic goiter, *i. e.*, the picture corresponds fairly well to the features that would have been seen prior to the treatment. So, when it has been emphasized that resection of the thyroid technically is more difficult in a thio-uracil-treated patient because here the gland is soft and markedly vascularized, this may hardly be due to any change in the thyroid brought about by the thio-uracil treatment, and it seems rather likely that the histological features of the gland will remain fairly unchanged under this treatment.

This view is also in keeping with the statement emphasized by *Jackson*[83]: that the histological picture of the thio-uracil-treated thyroid in primary thyrotoxicosis resembles the picture encountered before the treatment with Lugol's solution was introduced. In one case, *Rose & McConnell*[164] have performed biopsy of the thyroid prior to the institution of thio-uracil treatment and compared the histological features of the gland with those of the resected specimen from the same patient; and these authors state that the typical thyrotoxic changes in the gland persisted under the treatment. In contrast hereto, *Paschkis et al.*[153] found an increase in the hyperplasia under the same conditions. *Rawson, Evans, Means et al.*[155] performed biopsy of the thyroid on 5 patients prior to the thio-uracil treatment and found that 3 of them showed no distinct difference in the average height of the follicular cells before and after this treatment; in the remaining 2 patients, however, there was a difference and also an increased vascularization. In contrast to our observations, these authors state that hyperplasia of the lymphoid tissue in the thyroid is seen after thio-uracil treatment. In this connection it may also be mentioned that *Gargill & Losses*[59] have reported the case of a pa-

tient with thyrotoxicosis, in whom agranulocytosis appeared after protracted treatment with thio-uracil, and who died 6 days later. Histological examinations showed hyperplasia of the thyroid follicles, but no colloid and no lymphocytic infiltration.

In view of the assertion that the thio-uracil treatment gives no particular changes in the histological picture of the thyroid and has no influence on the acclerating factor, merely inhibiting the synthesis of thyroxin, it seems reasonable to assume that this treatment in itself has no direct curative effect.

It is a well-known fact that the quiet regimen of the hospital often gives a noticeable improvement in the thyrotoxic condition of such patients. Furthermore, through the thio-uracil treatment the organism may be brought into a state of complete quiescence, and by continued treatment this quiescent state may be maintained. It may be, then, that the accelerating factor or the impulses acting on the thyroid via inferior brain centers are abolished, so that recovery eventually may result. This will alter the histological picture of the thyroid, however, so that it should be possible histologically to decide whether the thyrotoxicosis is cured.

Chapter V

DOSAGE

Initial Dose.

The dosage of thio-uracil and methylthio-uracil has proved to be a question of very great importance, because these remedies in rather many patients produce some untoward effects, which sometimes may be of a very serious character.

When, in February 1944, we commenced in the Copenhagen County Hospital, Gentofte, to treat thyrotoxicotic patients with thio-uracil, we employed the initial dose given by *Williams & Bissell*[203], namely: 1.0—1.2 g daily, distributed over the entire day in single doses of 0.2 g. That just this amount was the proper dose had not been established with any degree of certainty, nor was there any theoretical foundation for it. At that point of time a few case reports had been published, stating that not only thio-urea but also thio-uracil might produce untoward effects in the patients. So it was fully realized that the question of dosage had to be dealt with very carefully.

The first 12 patients treated in this way were all given thio-uracil. In one case (see Fig. 50) we commenced with a daily dose of 1.0 g; in the remaining 11 cases the initial dose was 1.2 g. Thio-uracil and methylthio-uracil have always been given in the form of tablets of 0.2 g, and tablets with a lower content of the remedies have been employed only for maintenance dose. In altogether 4 cases, in which the treatment with thio-uracil was not sufficiently effective, the dose was increased to the maximum of 1.6 g daily (see Figs. 50 and 53) but no corresponding increase in the effects was observed. In one patient, the increase in the dose produced even an unexplainable aggravation of the thyrotoxic condition.

As mentioned before, the purpose of the experimental studies here reported was, among other things, to find some guiding principles for the clinical employment of these remedies — not least with regard to their dosage.

These experiments, which are reported in Part I, Chapter V, have shown that the strumogenic effect of thio-uracil as well as methylthio-uracil in rats at first increases with increasing dosage (from 1/4 mg daily for 15 days). Rather soon, however, the doses are reached that practically give the maximal effect on the weight of the thyroid and on its histological picture. Thus, 5 mg methylthio-uracil daily for 15 days gave an almost maximal effect (thyroid weight: 36.8 mg). On increasing the daily dose to 10 and 20 mg some increase was obtained in the strumogenic effect (thyroid weight 45.0 mg), but additional increase in the dose to 40 and 80 mg daily for 15 days gave merely a toxic effect on the animals and their body weight commenced to fall. Nor was there any increase in the thyroid weight; on the contrary, it showed a tendency to fall a little, probably on account of the toxic effect of such doses. Something similar was found to hold true of thio-uracil.

Of course, it is not justifiable offhand from these animal experiments to draw any conclusion about the effect of these substances on the human organism — among other reasons, because the dose employed, calculated per kg of body weight, is far greater in animal experiments than in their therapeutic employment. But our experiences with the 4 patients, in whom an increase in the thio-uracil dose gave no corresponding increase in the effect, correlated with the results of the animal experiments mentioned, suggest decidedly that the dose should not be increased as this very likely would increase the risk of untoward effects. Our present knowledge concerning this matter — that various factors may bring about a delay in the thio-uracil effect — gives a more solid foundation for this view.

The questions which then had to be solved were: 1) whether the clinical dose employed (1.0—1.2 g) was optimal, or whether a lower initial dose would prove just as effective; and 2) whether it was of any advantage to give the total daily dose in several small

doses in the course of the day rather than give the entire dose at once.

In order to answer the latter question, a certain dose of thio-uracil or methylthio-uracil was given to rats once a day for 15 days, and the effect of this on the thyroid weight and on the histological picture was compared with the effect obtained with the same daily dose distributed respectively on 2 and 3 equal doses in the course of the day. The results of these experiments showed (see Figs. 14 and 15) that distribution of the total daily dose on smaller doses gave a stronger effect on the thyroid of the rats, even though the difference was not particularly great. Still, these results appeared to justify the employment of several small daily doses in the treatment of patients.

No adequate answer may be given on the first question as far as thio-uracil is concerned, because the experimental studies have shown that methylthio-uracil has a considerably stronger strumogenic effect than has thio-uracil, while the toxicity of the two substances to rats differed but little. Consequently, in April 1944, we commenced using methylthio-uracil in the treatment of new patients. The results obtained with this remedy were so good that we have continued employing this substance, giving thio-uracil merely to the patients who already had been given this remedy from the beginning of the treatment.

Altogether 42 patients have been treated with methylthio-uracil, and in these cases the initial dose has been as follows:

9 patients: 1.0 g daily (0.2 g 5 times daily)
22 patients: 0.8 g daily (0.2 g 4 times daily)
11 patients: 0.6 g daily (0.2 g 3 times daily).

Here it proved impossible to make out any definite difference in the effectivity of the treatment in the patients who received 0.2 g methylthio-uracil 5 times daily and those who received this dose 4 and 3 times daily when the conditions that may delay the thio-uracil effect were taken into account. It may be that even a still lower initial dose will prove just as effective, but this cannot be settled here. It is to be emphasized, however, that even though the risk of untoward effects makes is desirable to give as small doses

as possible, we also have to consider the importance of getting the thyrotoxic state under control as soon as possible. Naturally, this applies chiefly to the severe forms of thyrotoxicosis.

It is to be mentioned here that in 3 of the patients treated with methylthio-uracil we likewise have tried to increase the dose in the beginning of the treatment, and — as was the case with thio-uracil — this gave no corresponding increase in the effect obtained.

Under the *continued treatment* with thio-uracil and methyl-thio-uracil we first employed preferably the procedure of continuing with the initial dose until the thyrotoxic state was under control and the metabolism had become normal. The time required for this may often amount to several weeks. Therefore — with a view to the untoward effects, which are more likely to appear within the first month of treatment — it is preferable to lower the daily dose by 0.2 — 0.4 g as soon as a clinical thio-uracil effect could be recognized distinctly, and the metabolism has shown a noticeable decrease. Then the daily dose was further decreased (to 0.2 g once a day) when the metabolism approached the upper normal limit, while at the same time there was an additional improvement of the thyrotoxic state of the patient (cf. Fig. 54). This procedure brought about, however, that the time which passed before the thyrotoxic state was completely under control, would sometimes be prolonged a little. It is to be emphasized that we never have followed any established schema of dosage; we have always individualized the treatment. The writer holds the view that individualization of the treatment of the patients here is of the greatest importance, as various factors may influence the course of the disease, and that in the thio-uracil treatment the principle must be as soon as possible to get down to the lowest suitable dose.

Maintenance Dose. — In adjusting the maintenance dose the principle must be to find the smallest amount of thio-uracil which in a given patient is able to suppress the thyrotoxic symptoms and keep the metabolism within normal limits. Sometimes this may be difficult because the amount of thyroid hormone required by the organism is not constant. The normal thyroid gland is able to set

free the amount of hormone that corresponds to the immediate requirement of the organism. In thyrotoxicosis, on the other hand, the thyroid is under the influence of a still unkown factor of acceleration, and it is practicable to lower the hormone production to a normal level only by means of an artificial inhibition of the synthesis of thyroid hormone (the thio-uracil effect). But when the amount of thyroid hormone required by the organism varies, this may readily bring about that a certain dose of thio-uracil in some periods will prove sufficient, in other periods too small or too large (see, for instance, Figs. 54 and 57).

Besides the thyrotoxic symptoms and the rate of metabolism, also the body weight of the patient has to be taken into consideration. For sometimes, also when the patient is kept on the maintenance dose, the body weight may increase quite considerably, in some cases even to absolutely undesirable values.

The *size of the maintenance dose* may vary from one patient to another, and often it varies in the individual patient too under the continued treatment.

When, under the introductory treatment, the thyrotoxic symptoms have subsided, and the metabolism has become normal we may choose between 3 procedures for further treatment:

1. Daily dosage (0.2—0.1—0.05 g once a day; see Fig. 54).
2. Discontinuous dosage (0.2 g every 2, 3 or 4 days; cf. Figs. 55 and 59).
3. A combination of 1 and 2 (cf. Fig. 56).

The experimental studies have shown:

1. When rats are treated with thio-uracil or methylthio-uracil, the difference in the effect on the thyroid from 10, 5, $2^1/_2$ and 1 mg daily is but rather slight. Only when the daily dose is cut down further ($^1/_2$—$^1/_4$ mg) does its effect decrease markedly (cf. Figs. 4 and 6).

2. The strumogenic effect of thio-uracil and methylthio-uracil on rats is far less pronounced when a certain dose is given every other day for 15 days than when one-half of this dose is given daily for 15 days (cf. Figs. 14 and 15).

The results of these experimental studies may be of considerable help in adjusting the maintenance dose, as this is liable to marked variation.

On lowering the daily maintenance dose from 0.2 to 0.1, 0.05 g or even less, it may be necessary either to have tablets made with different amounts of the remedy or to let the patient divide the

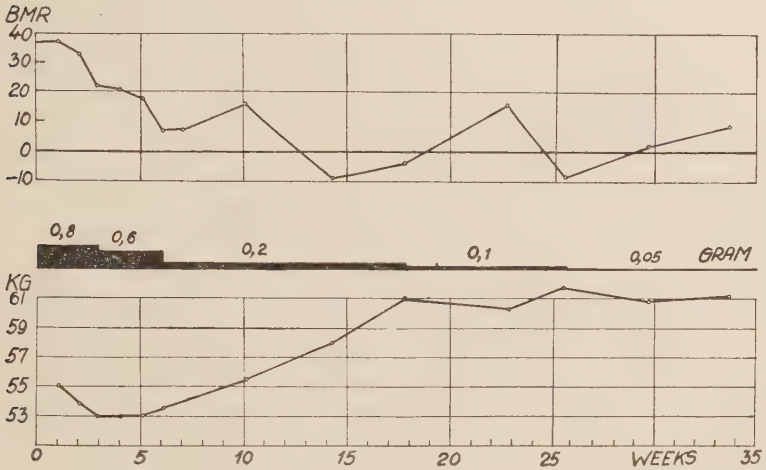


Fig. 54. Curves for dosage, body weight and metabolism in a woman, aged 52, with moderately severe type of thyrotoxicosis, treated with methylthio-uracil. (Patient No. 16).

tablet in several parts, which may readily compromise the accuracy of the dosage. On the other hand, it may be difficult for the patient to remember to take a tablet every third day.

In the treatment of our patients we have tried both procedures, but we have preferably employed the discontinuous dosage. Still, good results have been obtained with either procedure. It is to be mentioned too that in order to be able to vary the daily maintenance dose more accurately we have had tablets made, each of which contains 0.02 g methylthio-uracil.

The maintenance dose required by each individual patient will not be mentioned separately here. Figs. 54, 55, 56, 57 and 59 illustrate this individual variation very well. It is to be mentioned that one patient got along very well for several months on a dose

of 0.2 g methylthio-uracil every four days — which, according to the above, has to be looked upon as a very small dose; later on, however, this dose proved too small.

In some patients we several times have tried *discontinuance of*

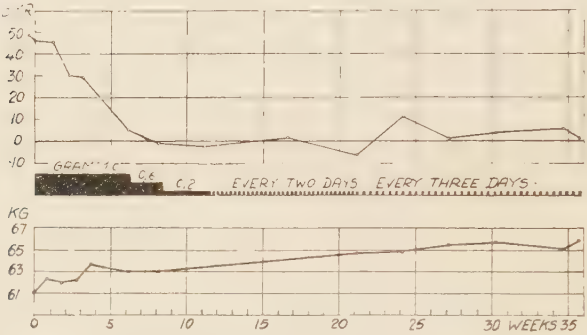


Fig. 55. Curves for dosage, body weight and metabolism in a woman, aged 39, with rather severe thyrotoxicosis, treated with methylthio-uracil. (Patient No. 33).

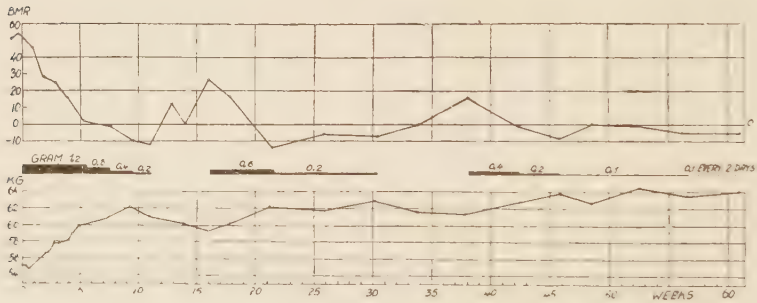


Fig. 56. Curves for dosage, body weight and metabolism in a woman, aged 41, with rather severe thyrotoxicosis, treated with thio-uracil. (Patient No. 2).

the thio-uracil treatment (see Fig. 56), but even after one year of treatment such discontinuance has resulted in a return of the thyrotoxic symptoms and increasing metabolism. Only in one patient have the thyrotoxic symptoms not returned — at this writing — 3 months after discontinuance of the treatment.

Overdosage. — At the institution of the thio-uracil treatment the patient should always be under regular observation, which

ought to be continued till the thyrotoxic state is under control. Until this is attained, the patients are often given large doses, which probably is the reason why the untoward effects most often appear in the first month of treatment. Of course, an overdosage of the remedy at this point of time is conceivable, but if the patient is under regular control, this will happen but very seldom and hardly ever go so far as to give clinical symptoms of hypothyroidism.

On the other hand, when the patient has been discharged from the hospital on some maintenance dose a possibility of overdosage will be present. Often a considerable length of time will pass between the control examinations and, furthermore, the thyroid hormone requirement of the organism is subject to variation. Finally it is to be emphasized that the optimal maintenance dose for the individual patient may vary considerably.

If the thio-uracil dose employed is too large, the supply of thyroid hormone to the organism will be too small, and gradually the rate of metabolism will fall to a subnormal level, while a state of myxedema at the same time will slowly develop.

When normal rats are given thio-uracil, the formation of thyroid hormone is inhibited, the metabolism of the rat decreases, and a state of hypothyroidism begins to develop. The anterior pituitary lobe tries by means of the thyrotropic principle to compensate this condition, which merely results in enlargement of the thyroid.

Something similar may reasonably be expected to occur in patients with thyrotoxicosis if the amount of thyroid hormone in the organism falls to subnormal values as a result of overdosage of thio-uracil.

These theoretical considerations have proved to hold true in practice.

In the preceding mention of the behavior of the goiter under thio-uracil treatment it was mentioned that in two patients the goiter increased in size under the treatment because of overdosage. It will be appropriate here to give a more detailed account of one of these patients.

Patient No. 52. Woman, 48 years old.

Clinical Diagnosis: Thyrotoxicosis; cardiac disease.

At the age of 20 years, uncomplicated rheumatic fever. Past history otherwise of no particular interest in this connection. The thyrotoxicosis had persisted for 3 months.

On admission, the patient bore the stamp of thyrotoxicosis (without exophthalmus). There was a moderate diffuse enlargement of the thyroid, which was of uniform, firm, elastic consistency.

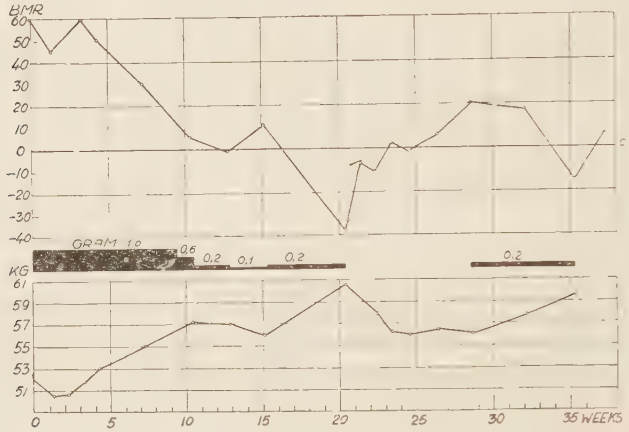


Fig. 57. Curves for dosage, body weight and metabolism in a woman, aged 48, with rather severe thyrotoxicosis, treated with methylthio-uracil (see the text).

Methylthio-uracil treatment was instituted (for dosage, see Fig. 57). Under this treatment the thyrotoxic symptoms subsided slowly. After about 10 weeks' treatment the patient was feeling perfectly well, though she still was a little nervous and had a slight degree of functional dyspnea.

At this juncture the patient was given a maintenance dose of 0.2 g daily. A couple of weeks later her condition was practically the same, and the maintenance dose was lowered to 0.1 g daily. 17 days later she was feeling perfectly well, with no complaints whatever, and she stated that it seemed to her that "her neck was getting thinner". But, as her rate of metabolism had increased from + 1 % to + 11 %, the maintenance dose was increased to 0.2 g daily.

5 weeks later she was readmitted for the sake of control examination. She now stated that 4 days after the preceding control examination she had had a severe cold with pronounced coryza and sore throat. When these symptoms subsided, she said her voice gradually commenced to change, becoming deeper and more coarse, and it was her impression that "her neck was

getting thicker", sometimes she had a sensation of "pressure on the windpipe" and difficulty in swallowing, and once she had an attack of suffocation. Her skin became more dry, her nails ceased growing, her hands and feet were very

A B

A B

Fig. 58. Woman, aged 48, with thyrotoxicosis, treated with methylthio-uracil (note the goiter).

A. After overdosage (myxedematous symptoms present; metabolism: — 38 %).

B. 4 weeks later, after discontinuance of the treatment.

cold, her "face was getting thicker" and her energy was decreasing. On readmission she appeared decidedly myxedematous, with a very large goiter of uniform firm consistency (see Fig. 58).

Now the metabolism was — 38 %, and the body weight had increased considerably (see Fig. 57).

The treatment with methylthio-uracil was discontinued, and on the following day the metabolism was — 34 %. After this, the condition of the patient was now undergoing a complete alteration but slowly. After a little over 2 weeks the metabolism reached a normal level, but it took one month before the myxedematous phenomena subsided completely.

The course of the disease in the case here reported fully confirms that often it may be very difficult to find the optimal maintenance dose.

Discussion.

It has been shown that in rats the antithyroid effect of a certain daily dose of thio-uracil increases when, instead of giving this dose at once, it is distributed over several smaller doses in the course of the day. The same findings have been reported by *Astwood*[16]. *Williams*[201] has illustrated the correctness of this aggravation by determination of the thio-uracil concentration in the blood and urine, finding that in both fluids the thio-uracil concentration is increased by this procedure; but he also states that with any dosage there is a pronounced lability of the thio-uracil concentration in the blood throughout the day.

The *initial dose* is given somewhat differently by the various authors. Nor is it generally agreed how long this dose is to be given or in how many smaller doses it has to be divided. For the sake of more easy survey of the procedures adopted by several authors in their dosage of thio-uracil and methylthio-uracil, the various procedures are presented schematically in Table 38.

TABLE 38.

Initial Dose as given by Various Authors.

Author	Remedy	Initial dose	Remarks
Astwood[15] (1943)	Thio-uracil	0.4—0.6 g	
Astwood[16] (1944)	—	0.3—0.6 g	In 2 daily doses. Dose generally reduced to 0.2—0.4 g within the first 4 weeks.

Author	Remedy	Initial dose	Remarks
Bartel[18, 19]	—	0.6 g	Preoperatively, until the thyrotoxic condition is fully under control.
Eaton[42]	—	0.6 g	Never necessary to give over 0.8 g daily.
Himsworth[78]	—	0.6 g	
Jackson[83]	—	0.1—0.2 g	(Often advisable to begin with small doses). Gradual increase to 0.4 g. This dose is reduced as soon as the thyrotoxicosis is under control.
McGavack et al.[118]	—	0.8—1.0 g	For 5—10 days, when metabolism is > + 50 % (0.2 g × 4—5). When metabolism is + 30— + 50% 0.6 g is given; at + 30 %: 0.4 g.
Nussey[148]	—	0.6 g	(0.2 g × 3) for 3—4 weeks. Then gradual decrease.
Palmer[152]	—	0.8 g	0.1 g every 3' hour for 3 days. 0.1 g every 4' hour for 3 days. Then 0.5—0.4 g daily till clinical improvement.
Paschkis et al.[153]	—	1.0 g	(0.2×5) till full improvement — then either 1) cessation until recurrence; intermittent treatment, or 2) maintenance dose.
Rose & McConnell[164]	—	0.6 g	(0.2×3) for 3—4 days — then 0.8—1.0 g (0.2 g×4—5) till distinct improvement or certainty of no effect.
Rawson, Evans et al.[155]	—	0.6 g	Preoperatively — decreasing to 0.4 g.
William[200]	—	0.6—0.8 g	
Williams[202]	—	0.4—0.6 g	Seldom necessary to give over 0.6 g. Then, after 2 weeks 0.3—0.4 g daily.

Author	Remedy	Initial dose	Remarks
Frisk[55]	Thio-uracil methylthio-uracil	0.4—0.5 g	Till objective improvement. Then gradual decrease of dose.
Meulengracht & Schmith[137]	Methylthio-uracil	0.75 g	25 cg × 3 for 1'—2' month. 25 cg × 1 for 2'—4' month. Great individual variations.
Westergaard[199]	—	1.0—1.2 g	Preoperatively until the day of operation.

There appears to be a tendency to reduce the doses given. Thus, in 1943 *Williams & Bissell*[203] employed 1.0—1.2 g thio-uracil for initial dose, whereas in 1944 *Williams*[202] states that this is too large, and that he finds 0.4—0.6 g more suitable.

When *McGavack et al.*[118] give an initial dose of 1.0—1.2 g thio-uracil, it is because, they claim, that in the more toxic patients it is desirable to make the metabolism decrease as soon as possible; it is to be mentioned, however, that the large doses are employed, at the most, for 10 days, even if the metabolism fails to decrease within this period. Some authors distribute the daily dose on many small doses. Thus, *Palmer*[152] begins with 0.1 g 8 times a day. *Williams*[202] likewise asserts that it is preferable to give the remedy every 3 hours, but that 3 times daily also gives satisfactory results. In contrast hereto, *Astwood*[16] claims that no particular advantage is derived from giving the remedy to the patients in more than 2 daily doses, finding the 12-hour interval very suitable.

Maintenance Dose. — As emphasized above, the maintenance dose varies from one patient to another, and in the individual patient it also is subject to variation from time to time. So it would be inpracticable to give any definite maintenance dose as the most suitable. According to *Nussey*[148], the maintenance dose is the smallest dose compatible with the well-feeling of the patient.

Several authors have found a maintenance dose of about 0.1—0.2 g daily to be suitable (*Donald & Dunlop*[39], *Eaton*[42], *Frisk*[55], *Palmer*[152], *Paschkis et al.*[153], *Rose & McConnell*[164], *Williams*[202]).

Astwood[16] gives 0.2 g, and the same dose is employed by *Mc Gavack et al.*[118], who add that 0.1 g daily nearly always has proved too small; in 18 patients they employed a maintenance dose of 0.2—0.4 g daily. On the other hand, *Thomson*[190] has used doses of 0.05 g daily.

For maintenance dose, *Meulengracht & Schmith*[137] give 12.5 cg methylthio-uracil daily, decreasing the dose to 12.5 cg twice a week. In view of the discontinuous dosage, this dose must be said to be extraordinarily small, but I have found it very serviceable myself (see above), whereas it appears not to have been employed by other clinicians.

On going through the present patient material I have noticed one striking feature: that the thyrotoxic symptoms regularly return on *cessation of the thio-uracil treatment*, even when this has been carried through for up to one year.

That the symptoms recur after treatment for a relatively short time is a well-known fact that has been emphasized by several authors, *e. g. Astwood*[15, 16], *Rose & McConnell*[164], *William*[200].

As mentioned before, however, several authors have observed that the symptoms did not return after treatment for about half a year. Of course, this may be due to the relatively small number of patients here observed, but to me it also suggests that perhaps the optimal maintenance dose still is not the absolutely minimal dose able to suppress the thyrotoxic symptoms, even though this holds true if only the risk of the untoward effects is taken into consideration.

It has been emphasized strongly that some of our patients who were kept on a small maintenance dose proved unable to stand a sudden mental or physical strain, as this might bring about a recurrence — although in a milder degree — of the thyrotoxic symptoms, especially the nervous. Possibly, in these patients, the maintenance dose has been too small. Likewise it may be that the explanation of the fact that the thyrotoxic symptoms have returned regularly when the remedy was discontinued after protracted treatment in several cases also is to be found in the maintenance

dose being too small, so that the required balance in the organism has not been kept up.

Sometimes it may be difficult to arrive at the proper maintenance dose. In one case (see Figs. 57 and 58) a daily dose of 0.1 g methylthio-uracil appeared to be too small, whereas 0.2 g daily for 5 weeks produced severe symptoms of *overdosage*, as pronounced myxedematous changes developed at the same time as the metabolism decreased to — 38 %. *McGavack et al.*[118] observed myxedematous phenomena in a patient who through 4 months was given 0.3 g thio-uracil daily as maintenance dose. In this case, however, the metabolism decreased merely to — 15 %. The symptoms commenced to subside 4 days after the discontinuance of the treatment, and one week later the metabolism was normal.

Also *Meulengracht & Schmith*[137] and *Paschkis et al.*[153] have reported cases in whom the appearance of myxedematous changes was due to overdosage. Like the writer, also the first-mentioned authors found the goiter to increase under the overdosage.

Finally, it is to be emphasized that there is no qualitative difference in the effect of thio-uracil and methylthio-uracil. But whether there be any quantitative difference in the effect of the two remedies under the treatment of thyrotoxicotic patients, is more difficult to say. Here it is merely to be pointed out that none of the authors employing thio-uracil have used so small maintenance doses as in the present patients treated with methylthio-uracil (*e. g.*, 0.2 g every 3 or 4 days, or in the patients treated by *Meulengracht & Schmith*[137] 12.5 cg twice a week).

Chapter VI

UNTOWARD EFFECTS

The thio-uracil treatment in cases of thyrotoxicosis means a great gain in the field of clinical medicine. Still, so far this form of treatment has met with a certain degree of reservation — chiefly because of its untoward effects, which by no means are rare phenomena.

In the present experimental studies (Part I) mention has been made of a good many investigations aimed, among other things, to disclose some noxious effects on rats from the administration of thio-uracil and methylthio-uracil under various experimental conditions. These substances were found to have a certain effect on the animals; and, when given in very large doses, they may prove fatal to the animal (see toxicity determinations in Part I, Chapter IV). When given subcutaneously or by mouth, even in large doses, however, no subsequent significant pathologic changes were seen in the animal organism that could not be ascribed to the anti-thyroid effects of these substances. Nor have such changes been reported in the literature — as far as I have been able to find out.

Considering that the doses employed in the animal experiments — calculated per kg of body weight — are much larger than the therapeutic doses usually employed in the clinic, the absence of toxic phenomena in the animals might perhaps be taken to suggest that these remedies would prove harmless in the human organism. Clinical experiments have clearly shown, however, that it by no means always is justifiable from animal experiments to draw decisive conclusions about the effect of the given substances in man.

On estimation of the serviceability of the thio-uracil treatment against thyrotoxicosis in man, the untoward effects that may be

produced by the treatment constitute a factor of very great significance. It is very important that attention be called to any *undesirable reaction* in the patients — no matter whether it seems insignificant or is of a more serious character, even though, of course, it cannot always offhand be ascribed to the treatment. So the term "undesirable reactions" is employed just because it does not imply that the changes observed are direct results of the treatment, whereas this is implied by the term "*untoward effects*".

If some undesirable reaction often appears in the patients under the treatment, it may convey some very valuable information. Thus, for instance, in no less than 19 of the present patients is was observed that under the treatment the white blood count once or several times has been under 4000, and that it usually and rapidly returned to normal values without any change in the dose. Therefore, it hardly will be fully justified offhand to designate this phenomenon as an untoward effect produced by the treatment.

It is to be emphasized at once that fairly severe untoward effects did not appear in any of the present 54 patients. A thorough review of this patient material shows, however, that one or more undesirable reactions were observed in no less than 37 out of the 54 patients treated with thio-uracil or methylthio-uracil. A greater majority of these phenomena were apparently of a quite harmless character, and they cannot all be said with certainty to have been brought about by the treatment.

Here no review will be given of each case presenting evidence of undesirable reactions; only a few patients will be mentioned separately. Nor will destinction be made between the patients who were treated with thio-uracil and those treated with methylthio-uracil. The purpose of the following investigation has been to see how often the individual undesirable reactions and untoward effects have been present in the patients under the thio-uracil treatment.

It is to be mentioned that in some of the cases several undesirable reactions were observed simultaneously or at different junctures in the course of the treatment.

Undesirable Reactions and Untoward Effects observed under the Thio-uracil Treatment of 54 Patients.

In 11 of these patients no undesirable reactions were observed. In the remaining 43 patients one or more undesirable reactions or untoward effects were observed as follows:

a.	Increase in the size of the goiter:	7 patients
b.	Rise in temperature:	7 —
c.	Gustatory disturbances:	4 —
d.	Nausea:	3 —
e.	Myalgia:	1 patient
f.	Arthralgia:	2 patients
g.	Exanthema:	4 —
h.	Edema:	3 —
i.	White blood count $<$ 4000:	19 —
	White blood count $<$ 3000:	4 —
	(Lowest value: 2040)	
k.	Platelet count $<$ 200.000:	28 —
	Platelet count $<$ 100.000:	3 —
	(Lowest value: 70.000)	

Ad a. The size of the goiter has been mentioned before. When the goiter in these 7 patients has increased in size, this reaction to the treatment cannot offhand be reckoned among untoward effects, as at any rate in 2 cases it was due to overdosage.

Ad b. After 18 days' treatment, *1 patient* had a rise in temperature, on which account the treatment was discontinued.

2 patients (mentioned separately on p. 197 and 201) had a rise in temperature accompanied by an acute aggravation of the thyrotoxic state, when an ineffective iodine therapy was discontinued and the thio-uracil treatment was instituted at the same time.

In the course of the first month *1 patient* had a rise in temperature, besides trombopenia and leukopenia. This patient was given operative treatment.

After 7 weeks' treatment, *1 patient* had a rise in temperature and at the same time the goiter increased considerably in size and became tender to touch (strumitis?).

After 12 days' treatment, *1 patient* had a rise in temperature, sore throat and redness of the fauces. On discontinuance of the treatment these symptoms subsided in 5 days. A couple of weeks later the patient

had an exanthema, edema and joint complaints. These symptoms subsided slowly when the dose was reduced.

After 12 days' treatment, *1 patient* had a rise in temperature, exanthema and edema (see Fig. 59).

Ad c. Gustatory disturbances (bitter taste, sweet taste, no taste at all) were observed in 4 patients after 15, 25, 41 and 41 days' treatment, respectively. These phenomena subsided each time the dose was lowered.

Ad d. After $3^1/_2$ months' treatment, *1 patient* had nausea and, simultaneously, an exanthema.

After 15 days' treatment, *1 patient* had nausea together with gustatory disturbances.

After 5 days' treatment, *1 patient* had nausea; a few weeks later leukopenia and thrombopenia.

Ad e. After 5 months' treatment, *1 patient* had transitory myalgia of the lower extremities and the loins; it subsided when the dose was reduced.

Ad f. After $2^1/_2$ months' treatment, *1 patient* had transitory swelling and tenderness of both ankles.

After 1 month's treatment, *1 patient* had transitory joint complaints together with exanthema and edema.

Ad g-h. After 1 week's treatment, *1 patient* had an itching skin eruption on the trunk and extremities; it subsided when the dose was reduced.

After 1 month's treatment, *1 patient* had an itching skin eruption together with edema (also joint complaints) which subsided slowly when the dose was reduced.

After 4 months' treatment, *1 patient* had a maculopapular, itching eruption on the trunk (together with nausea). It subsided without the dose being lowered (0.2 g every 3 days).

After 5 months' treatment, *1 patient* had edema (together with a considerable increase in the size of the goiter).

Finally, *1 patient* is to be mentioned more in detail:

Patient No. 1. Woman, 53 years old.

Clinical Diagnosis: Thyrotoxicosis (secondary); cardiac disease.

After 12 days' treatment with thio-uracil the patient had an exanthema + edema, together with a brief rise in temperature. The symptoms improved when the treatment was discontinued for one day; and they were aggravated when the treatment was resumed. Then an attempt was made with discontinuous treatment (see Fig. 59), but also this had to be stopped on account of the symptoms mentioned. At this juncture, the thyrotoxic symptoms had subsided almost completely, the metabolism had decreased to + 14 %, and the body weight was increasing (see Fig. 59). After cessation of the treatment the thyrotoxic symptoms

returned, while the exanthema and edema disappeared. After a few weeks, treatment with methylthio-uracil was tried; and this was tolerated without any inconvenience. The thyrotoxic symptoms disappeared. Since then, she has been given ambulatory treatment with this remedy. In spite of the low maintenance dose, she states emphatically that now she is feeling better than she has done for many years.

Ad i-k. In *1 patient*, after 4 weeks' treatment, the white blood count was 3080, the platelet count 100,000. At the same time the patient had a

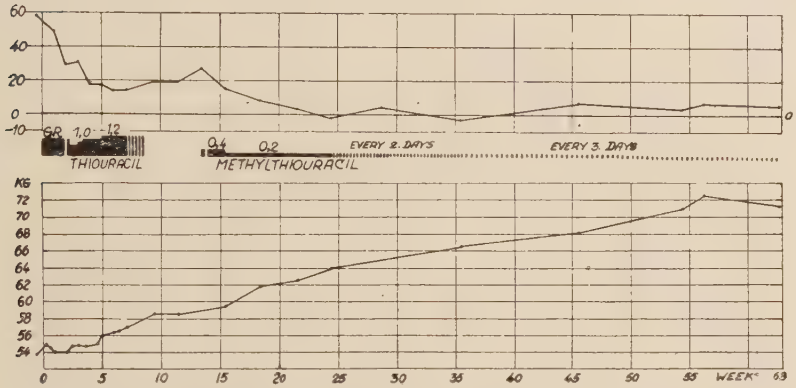


Fig. 59. Curves for dosage, body weight and metabolism in a woman, aged 53, treated with thio-uracil and methylthio-uracil (see the text).

transitory rise in temperature and nausea. Later, thyroidectomy was performed.

In *11 patients*, under the treatment, the white blood count fell below 4000, and the platelet count below 200,000, but no parellelism was seen between these counts except in the above-mentioned patient. On the other hand, 7 of these patients showed also some other undesirable reactions.

In *19 patients* the white blood count was less than 4000; and in 14 of these the subnormal values were demonstrated within the first month of treatment; in 6 of these patients subnormal values were again encountered later on under the treatment. Platelet counts of less than 200,000 were distributed more evenly under the treatment (see Figs. 42, 43, 44 and 45).

Subnormal values for the white blood count as well as for the platelet count have been followed regularly by a rise, generally without any change in the dosage. Clinical signs of leukopenia,

granulocytopenia or thrombopenia were never observed in this material; and the granulocyte count was never under 1000.

Discussion.

When it has been emphasized above that only 11 out of the 54 patients treated with thio-uracil or methylthio-uracil did not show any undesirable reactions under the treatment, this is by no means tantamount to observation of untoward effects from the treatment in 43 patients.

When in 28 patients, however, a platelet count under 200,000 was found, and in 19 patients a white blood count under 4000, this indicates that under the thio-uracil treatment the patients have a tendency to leukopenia and thrombopenia, even though the values mentioned cannot be set as fixed lower limits for normal values.

In *7 patients* a transitory fall in the white blood count below 4000 was the only undesirable reaction under the treatment. In *11 patients* a transitory fall in the platelet count to less than 200,000 was the only undesirable reaction. In *5 patients* both these phenomena were present under the treatment as the only undesirable reactions, without occurring at the same time.

It would hardly be justified offhand to speak of untoward effects in these 23 patients, especially in view of the fact that whenever a new examination was made it regularly showed an increase in the counts to normal values — without any change being made in the dose.

In *2 patients* the only undesirable reaction under the treatment was an increase in the size of the goiter resulting from overdosage. Nor would it be quite correct to designate this phenomenon as an untoward effect of the treatment.

Under the thio-uracil treatment of the remaining 18 patients, on the other hand, undesirable reactions were disclosed of such a character and in such a number that it seems justified to speak of untoward effects — a view that finds support in the fact that these by-effects regularly have subsided or disappeared when the dose was lowered or the treatment discontinued. As mentioned

before, none of these untoward effects have given rise to serious morbid conditions.

Nearly all authors who have employed thio-uracil treatment in thyrotoxicosis have sometimes noticed untoward effects in the course of the treatment.

As the untoward effects under thio-uracil treatment are of decisive importance in the estimation of the serviceability of the treatment, it will be appropriate here first to give a survey of these by-effects reported in the available literature, with references to the authors who have reported them. Only the untoward effects produced by thio-uracil or methylthio-uracil are included in this survey:

Rise in temperature: 9, 16, 18, 59, 78, 85, 92, 100, 108, 118, 137, 146, 153, 164, 199, 200.
Skin eruptions of various character: 19, 59, 78, 83 92, 100, 118, 137, 152, 153, 164.
Edema: 78, 83, 164, 203, 204.
Leukopenia: 6, 9, 16, 19, 59, 78, 92, 108, 118, 153, 154, 164, 167, 198, 199.
Granulocytopenia: 15, 42, 59.
Agranulocytosis: 16, 59, 78, 85, 100.
Lymphocytosis: 92, 118.
Thrombocytopenia: 78.
Changes in the histological features of the bone marrow: 59, 92, 118, 167.
Pharyngitis: 15, 85, 92, 108, 164.
Gingivitis: 118.
Conjunctivitis: 137.
Cephalalgia: 118, 199.
Nausea: 88, 108, 200:
Anorexia: 164.
Vertigo: 85.
Enlargement of lymph nodes: 57, 78, 118.
Swelling and tenderness of salivary glands: 59, 92.
Myalgia: 164.
Arthralgia: 153.
Jaundice: 59, 92, 118, 153.

Hematuria: 118, 152.
Crystaluria: 152.
Abdominal pains: 85.

The frequency of untoward effects under thio-uracil treatment appears to vary greatly in the materials reported by various authors.

A very thorough review of the course of the disease in each of our 54 patients shows that apparently definite untoward effects were ascertained in altogether 18 cases = *33* %. This figure is very high — considerably higher than those reported by other authors. Thus, *Frisk*[55] emphasizes that he has not yet seen any untoward effect under the treatment with methylthio-uracil.

Palmer[152] and *Eaton*[42] state that they have seen no serious by-effects during the treatment of 52 and 40 patients respectively, but they say nothing about how many of the patients showed slight by-effects. *Bartels*[18] (1944) did not observe any untoward effect in 11 patients under this treatment from 20 days to 6 months; in a subsequent report from 1945[19] he states that among 119 patients he had observed untoward effects only in 8 = 7 %. *Mc Gavack et al.*[118] reviewed the therapeutic results with a view to the occurrence of untoward effects among 135 patients, including 26 patients whom they had treated themselves, and found such effects in 16 = 12 %. Among 80 treated patients, *Meulengracht & Schmith*[137] found untoward effects in 8 = *10* %; they even state that no change in the blood picture was observed in these patients. Also *Astwood*[16] and *Williams*[202] state that untoward effects were found only in *10* % of the patients.

On the other hand, *Paschkis et al.*[153] found untoward effects in 5 out of 15 treated patients = *33* %. *Rose & McConnell*[164] found such effects in 8 out of 32 patients = *25* %. The latter authors state that they found severe leukopenia in 2 cases, and they emphasize that, in addition, 14 treated patients showed a tendency to a fall in the number of leukocytes. *Gargill & Lesses*[59] found by-effects in 8 out of 43 patients = *19* %. Finally, it is to be mentioned that *Leschly Jacobsen*[85] has treated 4 patients who all had untoward effects from the treatment.

The rather considerable divergent in the incidence of untoward effects as reported by the various authors appears not to be explainable by the size of the dose employed. This seems evident from Table 38, which gives the dosage employed by most of the authors mentioned here. Nor is the duration of the treatment very likely to play any particular rôle in this respect, because most of the untoward effects — as will be pointed out below — make their appearance in the beginning of the treatment. Possibly the cause of this divergent is to be looked for on the objective estimation of the cases, some clinicians taking some of the reactions to the treatment as untoward effects, while others have not assigned any importance to them.

The time for the appearance of the untoward effects is somewhat variable. These by-effects appeared to be able to set in at any juncture of the treatment. As a rule, however, the dose will be largest in the beginning of the treatment, and hence it is obvious to expect that the untoward effects will turn up more frequently in this period. In practice, indeed, this proves to hold true. In the present 54 patients the untoward effects appeared both shortly after the commencement of the treatment and after a considerable length of time, though chiefly within the first month of treatment. This is in keeping with the findings reported by *Astwood*[16] that the untoward effects make their appearance early; and he emphasizes that, consequently, they may hardly be signs of chronic toxicity. *Bartels*[19] states that the rise in temperature appears within the first 10 days of treatment, and *Westergaard*[199] found untoward effects in 3 patients after 11, 11 and 13 days' treatment respectively. Also *Meulengracht & Schmith*[137] have observed that the toxic symptoms appear within a short time after the institution of the treatment. *Himsworth*[78] distinguishing between overdosage and idiosyncrasy, emphasizes that the symptoms of the latter condition (fever, skin eruption, enlargement of lymph nodes, edema, and changes in the blood picture) appear after 1—2 weeks' treatment, not under the maintenance therapy.

Still, several authors have observed untoward effects even after protracted treatment; and it is to be mentioned that *Gargill &*

Lesses[59] have reported that in one patient, who had been treated through a considerable length of time with small doses of thio-uracil (0.2 g daily), they observed a sudden appearance of agranulocytosis which terminated fatally in 6 days.

According to *Astwood*[16] threatening danger of untoward effects is revealed most reliably by the complaints and temperature of the patient. He mentions that patients liable to allergic reactions possibly are more inclined to become hypersensitive to thio-uracil. *McGavack et al.*[118] state that fever and skin eruption seem to be brought about by hypersensitiveness rather than by a cumulative toxic effect.

Changes in the blood picture under the thio-uracil treatment appear not only to be among the most frequent untoward effects, but are undoubtedly to be looked upon as the most serious. As mentioned, in 19 of our patients a transitory fall in the white blood count to less than 4000 was observed once or more times. The same tendency was frequently observed by *Rose & McConnell*[164] and by *Palmer*[152]. But, as mentioned, a transitory fall in the number of white blood cells is hardly to be looked upon as an untoward effect. This view has been emphasized also by *Astwood*[16] who says that there are mild forms of untoward effects that cannot with certainty be ascribed to the thio-uracil given; this applies, for instance, to the fall in the white blood count that is followed by a rise, in spite of the continuation in the treatment. *Astwood*[16] also states that apparently the number of leukocytes often is low in thyrotoxicosis. *McGavack et al.*[118] likewise mention that often it is difficult with certainty to characterize a moderate leukopenia with relative lymphocytosis as toxic phenomena; they state that such changes hardly require discontinuance of the treatment, but still a reduction of the dose. *Palmer*[152] discontinues the treatment for at least 72 hours, however, when the white blood count falls to 4000. Our own therapeutic results show that this may hardly be necessary; on the other hand, I think, it is important to perform a differential count, when the white blood count falls to 4000. *Eaton*[42] makes a differential count when the white blood count falls to 3500.

More severe forms of leukopenia have been observed by *McGavack et al.*[118], *Rose & McConnell*[164] *and Rubenstein*[167]. Further, *Kahn & Stock*[92] have reported the case of a patient with fatal leukopenia.

The purpose of the differential count is to disclose whether the leukopenia is accompanied by a threatening fall in the granulocyte count. In our material, as mentioned before, granulocytopenia was observed in 3 patients, but each time these changes were transitory. In contrast to this, agranulocytosis has been observed by *Kristiansen*[100] and *Leschly Jacobsen*[85], and agranulocytosis with fatal outcome has been reported by *Gargill & Lesses*[59], *Himsworth*[78] and *Lundbæk*[108]. *Haler*[67] warns strongly against the employment of thio-uracil, stating that fatal agranulocytosis has been brought about by this substance af least in half a dozen cases. In this connection, it is also to be mentioned that *Himsworth*[78] has observed leukopenia to appear very suddenly in patients who previously showed a normal blood picture. In the case reported by *Gargill & Lesses*[59] the agranulocytosis likewise set in suddenly.

On *examination of the bone marrow* we have observed a lively activity in the myelocytic system as well as in the erythrocytic — but, apart from this, no definite abnormality. *McGavack et al.*[118] have observed a fall in the myeloid series of cells and an increase in lymphocytes, hematogonia and reticulum cells. In a patient with severe leukopenia, *Rubenstein*[167] found cessation of maturing, together with hypoplasia of the myeloid elements. In a patient who died with severe leukopenia after thio-uracil treatment, *Kahn & Stock*[92] found the granulopoietic series to be greatly reduced. In keeping with these observations, *Gargill & Lesses*[59] state that the toxic effect of thio-uracil on the bone marrow appears to be characterized by disappearance of mature granulocytes. The authors emphasize that this possibly is due either to 1) a disturbance in the maturing of promyelocytes or to 2) a direct destruction of cells after the promyelocytic stage. They mention the possibility of a similar destruction of granulocytes taking place in the blood stream.

Finally, it is to be mentioned that altogether 4 authors[59, 92, 118, 153] observed *jaundice* under the treatment. In the case reported by

Kahn & Stock[92] the patient died, but the autopsy gave no anatomical explanation of the jaundice, which, according to the authors, appears to be explainable on the basis of toxic hepatosis. *Gargill & Lesses*[59] have reported the case of a patient who became jaundiced after 3 weeks' treatment. The condition of this patient did not improve, however, after cessation of the treatment; on the contrary, the icterus index rose to 180, on which account the patient was submitted to operative treatment, as the authors took it to be an instance of obstructive jaundice. But the operative result was negative and biopsy of the liver showed acute biliary stasis without hepatitis.

From the findings cited above, it will be evident 1) that untoward effects under the thio-uracil treatment are by no means rare phenomena, and 2) that these by-effects may appear at any juncture of the treatment, though they are more frequent in the beginning. Severe by-effects appear to be rather rare. Some patients seem to have a certain degree of hypersensitiveness to thio-uracil

A very close control with the patients who are treated with thiouracil or methylthio-uracil has to be considered absolutely required. This control should be aimed, above all, at the blood picture of the patient. With a view to the possibility of the untoward effects, the aim should be to give the patient the smallest dose of the remedy capable to check the state of thyrotoxicosis.

CONCLUSION

Treatment of thyrotoxicosis with thio-uracil and methylthio-uracil means a considerable advance in internal medicine and surgery. Experimentally these substances are not particularly toxic to animals. Clinically, owing to their antithyroid effect, they are able with a fairly high degree of regularity to make the symptoms of thyrotoxicosis subside or disappear completely, and possibly they may indirectly bring about recovery from this disease.

Furthermore, the two remedies are of great value in cases where iodine therapy has proved ineffective. Besides, combined with iodine therapy they are highly suitable for the preoperative treatment, reducing the risk of thyrotoxic crisis.

The frequent appearance of untoward effects under the treatment with these remedies, however, requires that the patients should be watched closely, especially with regard to changes in the blood picture. As the untoward effects are particularly apt to appear within the first month of the treatment, when the largest dose is employed, it is desirable that this treatment be commenced in the hospital.

In future the efforts will have to be aimed at the finding of remedies with the same therapeutic effect, but without toxic effect on the human organism.

RESUMÉ

Formaalet med det foreliggende arbejde er gennem experimentelbiologiske og kliniske undersøgelser at bedømme tiouracilvirkningens indflydelse paa den dyriske organisme og paa patienter med thyreotoxicosis.

Arbejdet blev paabegyndt i januar maaned 1944 paa en tid, da Danmark var afskaaret fra det normale, videnskabelige samkvem med andre lande. Meddelelser bl. a. af *Mackenzie, Mackenzie & McCollum*[120], *Astwood*[15] og *Williams & Bissell*[203] viste, at visse svovlholdige, kemiske forbindelser, særlig sulfaguanidin, tiourinstof samt tiouracil paa forsøgsdyr fremkaldte struma + hyperplasi of thyreoideas parenchym. Samtidig indtraadte en hypothyroid tilstand hos dyrene. Overfor patienter med thyreotoxicosis foraarsagede tiourinstof og tiouracil, at de thyreotoxiske symptomer aftog.

Da den tilgængelige litteratur var sparsom, blev der i dette arbejde lagt særlig vægt paa saadanne forsøg, der kunde være vejledende for anvendelsen af stofferne i klinikken.

Den ved arbejdets afslutning foreliggende, tilgængelige litteratur er omhyggeligt gennemarbejdet.

Kapitel I.

Strumaproblemet omtales, og der gives en kortfattet oversigt over faktorer, der har betydning for udviklingen af struma hos forsøgsdyr. Jodets betydning for opstaaelsen af struma diskuteres. *Chesney, Clawson & Websters*[31] opdagelse af kaalens strumogene effekt gav anledning til en lang række undersøgelser; som et resultat af disse naaede *Kennedy*[94] frem til den formodning, at et

tiourinstofderivat var den strumogene faktor i rapsfrø. Samtidig hermed gjorde *Richter & Clisby*[162] den iagttagelse, at fenyltiourinstof paa-rotter fremkalder hypertrofi og hyperplasi af thyreoidea, en virkning, som *Mackenzie, Mackenzie & McCollum*[120] ligeledes ret tilfældigt kunde paavise hos sulfaguanidinet.

Kapitel II.

Fremgangsmaaden ved forsøgene gennemgaas. Som forsøgsdyr er anvendt albinorotter. Hos marsvin indtræder thyreoideaforandringerne ikke indenfor en rimelig tid, hvorfor disse dyr er uanvendelige.

Netop udvoksede (6 mdr. gamle) rotter med en legemsvægt paa ca. 200 g er fundet velegnede; thyreoideaforandringerne indtræder hurtigt hos disse. ♀- og ♂-rotter reagerer ens. ♀-rotter synes at taale den anvendte, perorale doseringsmaade bedst (øsofagussonde). For saa vidt muligt at gøre de forskellige forsøg sammenlignelige er disse dyr (6 mdr.s ♀-rotter) derfor fortrinsvis anvendt. I enkelte forsøg er subcutan dosering anvendt, virkningen herved er lidt stærkere end efter peroral indgift. Intraperitoneal dosering er anvendt ved toxicitetsforsøg.

Kapitel III.

40 svovlholdige, kemiske forbindelsers strumogene effekt overfor 6 mdr.s ♀-rotter undersøges. Formaalet er at finde stoffer med stærkere antithyroid virkning end tiouracil. Som kriterier for stoffernes virkning anvendes thyreoideas vægt og histologiske billede. Tiourinstofderivater, pyrimidiner samt tiohydantoiner er fortrinsvis undersøgt.

26 af de undersøgte stoffer er ikke omtalt i den tilgængelige litteratur. 25 af de 40 undersøgte stoffer havde strumogen virkning i stærkere eller svagere grad. Følgende 8 stoffer havde en stærkere virkning paa thyreoidea end tiouracilet: 1.) 2-tio-4-metyl-6-oxypyrimidin. 2) 2-tio-4-fenyl-6-oxypyrimidin. 3) 2-tio-4-benzalhydantoin. 4) N,N'-ætylentiourinstof. 5) 2-tio-hydantoin. 6) 2-tio-acetylhydantoin. 7) 2-tio-4-eddikesyre-6-oxypyrimidin. 8) 2-tio-6-oxy-tetra-hydrochinazolin. Stofferne er opstillet efter graden af deres thyreoideavirkning med faldende styrke fra 1 til 8.

Metyltiouracil er det mest effective af samtlige undersøgte stoffer.

En sammenligning mellem stoffernes kemiske konstitution og strumogene effekt viser, at tilsyneladende smaa variationer i den kemiske konstitution kan have afgørende betydning for den strumogene effekt.

Svovl er til stede i alle stærkt eller svagt virkende stoffer, der er undersøgt. C:S-radikalet er til stede i alle stærkt virkende strumogene stoffer. Substitutionen med en aminogruppe afsvækker eller ophæver den strumogene virkning.

Kapitel IV.

Toxicitetsforsøg. Dosis minima letalis (d. m. l.) bestemmes for tiouracil, metyltiouracil og fenyltiouracil. *Dosis* er givet intraperitonealt fordelt paa 2 lige store doser i 2 paa hinanden følgende dage.

Resultater: d. m. l. — tiouracil: 350—400 mg.
d. m. l. — metyltiouracil: 300—320 mg.
d. m. l. — fenyltiouracil: > 400 mg.

Undersøgelserne i dette og forrige kapitel medførte, at metyltiouracil af forfatteren blev anvendt i klinikken overfor thyreotoxicosis og efterhaanden erstattede tiouracil.

Tiourinstoffets virkning paa forsøgsdyr omtales. Bestemmelse af d. m. l. for dette stof synes uigennemførlig. En del af forsøgsdyrene (rotter) synes at være overfølsomme overfor tiourinstof og dør efter *en enkelt* lille dosis (7—8 mg), medens andre dyr taaler 80—160 mg.

Tiourinstof findes langt mere toxisk overfor forsøgsdyr end tiouracil, metyltiouracil og fenyltiouracil; forfatteren har derfor ikke anvendt det i klinikken overfor thyreotoxicosis.

Kapitel V.

I dette kapitel foretages nærmere undersøgelser over tiouracilets og metyltiouracilets virkning paa thyreoideas vægt og histologiske billede hos rotter under følgende forsøgsbetingelser (hvor der intet særligt er anført, har man benyttet 6 mdr.s ♀-rotter):

1. stigende dosis (1/4—80 mg daglig) i 15 dage peroralt.

2. konstant dosis (tiouracil 10 mg, metyltiouracil 5 mg) daglig i et stigende antal dage (2—40 dage) peroralt.
3. varieret dosering (samme dagdosis gives i een eller flere injektioner daglig, hveranden eller hvertredie dag etc. i 15 dage) peroralt.
4. efter afsluttet behandling med 5 mg metyltiouracil daglig i 15 dage peroralt.
5. efter langvarig (ret svag), subcutan tiouracilbehandling fra 12' til 205' levedag.

ad 1:

Thyreoideavægten stiger jævnt — er paa det nærmeste maximal efter 80 mg tiouracil og 20 mg metyltiouracil. Vægten er her en logaritmisk funktion af dosis størrelse. Samtidig faas en jævn stigning af thyreoideas histologiske aktivitet. Der er ret nøje overensstemmelse mellem tiouracilvirkningen paa thyreoideas vægt og histologiske aktivitet.

ad 2:

Thyreoideavægten stiger efter et par dages forløb og er paa det nærmeste maximal efter 20 dages behandling. Vægten er her en logaritmisk funktion af behandlingens varighed. (Metyltiouracil virker langt stærkere end tiouracil). Samtidig faas en jævn stigning af thyreoideas histologiske aktivitet. Tegnene paa forøget histologisk aktivitet indtræder før vægtstigningen; der er iøvrigt ret nøje overensstemmelse mellem tiouracilvirkningen paa thyreoideas vægt og histologiske aktivitet.

ad 3:

Thyreoideavægten øges, omend i ringe grad, naar den daglige totaldosis fordeles paa flere enkeltdoser i løbet af dagen. Tiouracilvirkningen formindskes derimod *meget betydeligt*, naar samme (eller dobbelte) totaldosis gives som enkelt dosis hveranden eller hvertredie dag. Der er ret nøje overensstemmelse mellem tiouracilvirkningen paa thyreoideas vægt og histologiske aktivitet.

ad 4:

Thyreoideavægten aftager jævnt efter afsluttet metyltiouracilbehandling, men stiger atter sekundært (efter 1—3 mdr.s forløb)

til ca. det dobbelte af kontrolvægten; ogsaa her findes ret nøje overensstemmelse mellem thyreoideas vægt og histologiske aktivitet.

ad 5:

Thyreoideas vægtstigning efter den langvarige behandling er sammenlignet med kontroldyrene: hunrotter: 350 %; hanrotter: 500 %. Tegnene paa histologisk aktivitet i thyreoidea varierer fra moderate til maximale. Forsøget viser, at thyreoidea (selv under langvarig behandling) ikke er i stand til at overvinde tiouracilets antithyroide virkning.

Kapitel VI.

Metyltiouracilbehandlingens indflydelse paa rotters (6 mdr.s ♀-rotters) stofskifte bestemmes under følgende forsøgsbetingelser:

1. stigende dosis (1—40 mg daglig) i 15 dage peroralt.
2. konstant dosis (5 mg daglig) i et stigende antal dage (3—42 dage) peroralt.
3. efter afsluttet behandling med 5 mg metyltiouracil daglig i 15 dage.

Kontrolforsøg (basalstofskiftebestemmelser) viser, at 6 mdr.s ♀-rotter forbruger gennemsnitlig 110 ml O_2 pr. minut og m^2 overflade.

ad 1:

Stofskiftet falder jævnt til ca. 50 (efter 40 mg i 15 dage). Stofskiftet er her en logaritmisk funktion af dosis størrelse.

ad 2:

Stofskiftet falder jævnt til ca. 72 (efter 42 dages behandling). Stofskiftet er her en logaritmisk funktion af behandlingens varighed.

ad 3:

Stofskiftet stiger jævnt (men langsomt) efter ophort metyltiouracilbehandling, men falder atter sekundært (efter 1—3 mdr.s forløb) til ca. 66.

Overensstemmelsen mellem tiouracilvirkningens indflydelse paa thyreoideas vægt og histologiske aktivitet samt paa stofskiftet fremhæves. Endvidere diskuteres aarsagen til, at der efter afsluttet

behandling med metyltiouracil sekundært indtræder: 1. vægtstigning af thyreoidea, 2. forøgede tegn paa histoligsk aktivitet i thyreoidea og 3. stofskiftefald.

5 mg metyltiouracil daglig reducerer som vist rotternes stofskifte ca. 33 %. Det vises, at stofskiftet hos thyreoidectomerede rotter reduceres ca. 30 % i løbet af ca. 40 dage efter operationen. Dette viser, at metyltiouracilets hæmmende virkning paa thyreoideas hormonproduktion har været komplet. 60 dage efter thyreoidectomien har de samme rotter faaet 20 mg metyltiouracil daglig i 15 dage peroralt, uden at stofskiftet derved er nedsat yderligere, hvilket viser, at thyreoidectomien har været total.

Kapitel VII.

Der foretages en række undersøgelser over tiouracilvirkningens indflydelse paa den øvrige del af rottens organisme. Undersøgelserne skal ses i sammenhæng med de i II del, kapitel IV omtalte laboratorieundersøgelser paa thyreotoxicosepatienter behandlet med tiouracil og metyltiouracil.

1:

Det vises experimentelt, at en konstant, men let tiouracilvirkning (subcutan dosering — stigende dosis — 3 gange ugentlig) ikke hæmmer væksten hos rotter, der behandles fra 12' til 205' levedag; dyrenes almentilstand paavirkes tilsyneladende heller ikke paa noget punkt. Store doser tiouracil og metyltiouracil (80 mg) nedsætter derimod rotternes legemsvægt allerede i løbet af 15 dage (toxisk virkning).

2:

Løbehjulsforsøg viser, at rotternes energi og muskelaktivitet viser tendens til at falde (overensstemmende med den fremkaldte hypothyroide tilstand), naar dyrene behandles med 5 mg metyltiouracil gennem 1—3 maaneder.

3—4—5:

Efter middelstore doser tiouracil (10 mg) eller metyltiouracil (5 mg) daglig i 40 dage (peroralt), samt efter store doser tiouracil eller

metyltiouracil (80 mg daglig, peroralt) i 15 dage findes ved histologisk undersøgelse ingen patologiske forandringer i rotternes knoglemarv, milt, lever eller nyrer. Efter samme behandling findes ved histologisk undersøgelse af hypofysen en normal cellulær opbygning uden degenerationstegn. Hypofysevægten hos rotterne ligger imidlertid lidt højere end gennemsnitsvægten hos kontroldyrene. Behandlingen har heller ingen paaviselig indvirkning paa ovarie- eller uterinvægt, og ovariernes histologiske billede er normalt efter behandlingen; samme resultat faas ogsaa ved mindre doser. Hos hun- og hanrotter, der fra 12' til 216' levedag har været underkastet en konstant, men let tiouracilpaavirkning, findes ingen afvigelse fra det normale i antallet af hvide blodlegemer, ligesom differentialtælling af hvide blodlegemer viser normale forhold.

Endelig vises det, at 4 ugers behandling med 10 mg tiouracil daglig peroralt ikke fremkalder forandringer i 6 maaneder gamle hunrotters brunstcyklus.

6:

Da der hos thyreotoxicosepatienter, behandlet med tiouracil eller metyltiouracil, er fundet ret lave værdier for serumkalkindholdet, er tiouracilvirkningens indflydelse paa rotternes serumcalcium- og serumfosfatindhold undersøgt.

Hos saavel hun- som hanrotter, der har været underkastet en konstant, men let tiouracilpaavirkning fra 12' til 216' levedag, fandtes ingen sikre afvigelser fra det normale hverken i serumcalcium- eller serumfosfatværdierne. Hos de samme dyr viste røntgenfotografering af underextremiteternes knogler fuldstændig normale forhold.

Kapitel VIII.

Tiouracilets forhold i organismen omtales, det paavises, at stoffets virkning paa thyreoidea er mere udtalt efter subcutan end efter peroral dosering, et forhold som kan tyde paa større resorption fra subcutis end fra tarmkanalen, muligvis betinget af større destruktion i denne. Den foreliggende litteratur om resorptionen af tiouracilet og tiouracilets forhold i blodet, samt fordelingen i

den øvrige organisme, gennemgaas. Endvidere omtales udskillelsen af stoffet fra organismen og destruktionen i organismen. Det vises, at virkningen paa thyreoidea øges, naar en bestemt mængde tiouracil eller metyltiouracil i stedet for at gives i en enkelt dosis fordeles over flere doser i løbet af dagen, og at virkningen endvidere falder stærkt, naar den samme totaldosis gives hveranden eller hvertredie dag. Disse forhold maa betyde, at tiouracilkoncentrationen i thyreoidea hurtigt aftager efter indgiften, hvoraf man kan slutte, at det samme er tilfældet med koncentrationen i blodet. Om dette hurtige fald i blodkoncentrationen skyldes omdannelse i eller udskillelse fra organismen, har forfatteren ikke undersøgt.

Kapitel IX.

I dette kapitel gives en kortfattet oversigt over vekselvirkningen i det endokrine glandelsystem, idet kendskab hertil er nødvendigt for forstaaelsen af tiouracilvirkningen paa thyreoidea. Balancetilstanden mellem de endokrine glandler, særlig mellem thyreoidea, hypofyse og ovarier, omtales, og det vises ud fra litteraturen, hvorledes en forskydning i denne balancetilstand, for eksempel mellem thyreoidea eller ovarier og hypofyseforlap, kan hæmme eller stimulere hypofyseforlappens hormonproduktion.

Det vises experimentelt, at den øgede produktion af thyreotropt hormon under tiouracilbehandling i kendelig grad kan hæmmes ved store doser østrin. Endvidere omtales, at forfatteren med østrin har været i stand til at hæmme den kompensatoriske hypertrofi i den tilbageblevne thyroidealap hos hemithyreoidectomerede rotter.

En nedsættelse af østrinmængden i organismen kan ikke blot give anledning til forøget udskillelse af gonadotropt hormon, men ogsaa af thyreotropt hormon (klimakteriel thyreotoxicosis). Da det endvidere med thyreotropt hormon experimentelt er muligt at fremkalde en thyreotoxicoselignende tilstand hos forsøgsdyr, kan det ikke udelukkes, at dette hormon ogsaa forefindes i forøget mængde hos patienter med (almindelig) thyreotoxicosis, selv om det ikke er lykkedes at paavise dette i forøget mængde her. Spørgsmaalet diskuteres. Da thyreotoxicosens ætiologi imidlertid er

ukendt, har forfatteren foretaget en række hormonanalyser paa døgnurin (serieundersøgelser) fra unge patienter med thyreotoxicosis. Hos alle patienter har hormonindholdet (gonadotropin, østrin, testishormon) vist værdier, der ikke afviger fra normalværdierne.

Behandlingen af patienter med østrin med det formaal at undertrykke en hyperfunktionstilstand i hypofyseforlappen omtales.

Kapitel X.

I dette kapitel gives en oversigt over den tilgængelige litteratur vedrørende tiouracilets virkningsmekanisme. Thyreoideahormonet og thyreoideas jodoptagende evne omtales, ligesom jodets syntetisering til thyroxin i glandlen og udenfor denne diskuteres. Jodmangel i organismen fører til strumadannelse med hyperplasi af thyreoideavævet, forandringer, der svarer til thyreoideaforandringerne ved tiouracilbehandling. Det vises experimentelt, at jodtilførsel samtidig med indgift af en middelstor dosis metyltiouracil hos rotter er i stand til i mærkbar grad at nedsætte tiouracilvirkningen paa thyreoidea. Jodvirkningen gør sig dog her næsten udelukkende gældende paa det histologiske billede, hvorimod strumadannelsen ikke paavirkes i større udstrækning. Undersøgelserne viser imidlertid, at thyreoidea er i stand til at optage jod trods behandling med metyltiouracil, samt at angrebspunktet for jod og thyreotropt hormon er forskelligt. Under en gennemgang af litteraturen vises det, at tiouracilet er i stand til om ikke at hindre, saa dog at hæmme jodoptagelsen, samt gribe hæmmende ind paa syntetiseringen af jod til dijodtyrosin og thyroxin, en proces, som synes at være af enzymatisk natur. Maaden, paa hvilken denne hæmmende virkning foregaar, er endnu ikke fuldt opklaret.

Resultatet af tiouracilbehandlingen paa rotter maa anses for at være en nedsættelse af thyreoideahormonmængden i organismen. Det vises experimentelt, at thyroxin hindrer tiouracilets virkning paa thyreoidea, hvorfor tiouracilet ikke kan have virkning paa færdigdannet thyroxin. En thyroxinproduktion udenfor thyreoidea kan ikke udelukkes, men tidligere omtalte forsøg med behandling af thyreoidectomerede rotter med metyltiouracil viser, at thyroxin, som eventulet dannes udenfor thyreoidea, enten maa

være fysiologisk inaktivt eller at tiouracilet, saafremt thyroxinet er fysiologisk aktivt, ikke har nogen hæmmende virkning paa dets dannelse.

Den manglende virkning af tiouracilet paa færdigdannet thyreoideahormon maa anses for at være aarsagen til, at tiouracilet tilsyneladende er uden virkning paa marsvin og først efter langvarig behandling gør sin virkning gældende paa mennesker med normal thyreoideafunktion.

II Del

Kliniske undersøgelser.

Kapitel I.

I indledningen omtales uoverensstemmelsen i litteraturen vedrørende thyreotoxicosens nomenklatur. Forfatteren har valgt betegnelsen: thyroetoxicosis som en fællesbetegnelse for samtlige tilstande i organismen, der er foraarsaget af en patologisk hyperfunktion af glandula thyreoidea. Endvidere omtales vanskeligheden ved at inddele den thyreotoxiske tilstand i forskellige grupper, et forhold, som forfatteren heller ikke i det foreliggende arbejde har forsøgt paa, og som heller ikke anses for vigtigt i denne forbindelse, hvor formaalet først og fremmest er en paavisning af tiouracilvirkningen paa den thyreotoxiske tilstand. Forudbestaaende forandringer i thyreoidea (sekundær thyreotoxicosis) samt recidivtilfælde synes dog at have afgørende betydning.

Formaalet med den kliniske del af dette arbejde er at undersøge tiouracilvirkning paa den thyreotoxiske tilstand som helhed, samt paa thyreotoxicosens vigtigste symptomer og følgetilstande *indenfor det første aar.* Endvidere at bedømme tiouracilets virkning paa organismen med særligt henblik paa bivirkninger, samt tilrettelægge den rette dosering.

Patientmaterialet gennemgaas. 12 patienter er behandlet med tiouracil, 42 med metyltiouracil. Behandlingstiden varierer fra 1 maaned til godt 1 aar. Patientmaterialet er usorteret og omfatter saavel primære som sekundære former af thyreotoxicosis samt

recidivtilfælde. Patienternes alder varierer fra 21—71 aar. Ialt er 7 mænd og 47 kvinder behandlet.

Kapitel II.

Formaalet med dette kapitel er udelukkende at bedømme tiouracilvirkningens kliniske effekt overfor thyreotoxicosis som helhed.

Hos de 54 behandlede patienter kunde en sikker tiouracilvirkning erkendes hos 47. Hos 7 kom der ingen sikker virkning. Af disse 7 var 4 dog kun behandlet i ret kort tid. Ved en gennemgang af ialt 595 patienter, der er omtalt af 21 forskellige forfattere, viste det sig, at tiouracilvirkningen kun var uden effekt hos 12 patienter, af hvilke 6 ligeledes var kortvarigt behandlet. Man anser det for berettiget at slutte, at tiouracilvirkningen, saafremt tilstrækkelig langvarig behandling er gennemførlig, vil gøre sig gældende overfor den thyreotoxiske tilstand hos mere end 90 % af patienter med thyreotoxicosis.

Kapitel III.

I dette kapitel gøres rede for tidspunktet for tiouracilvirkningens indtræden. Vanskelighederne ved at bedømme dette tidspunkt fremhæves og diskuteres; forfatteren har valgt at anvende virkningen paa saavel stofskifte som vægt i forbindelse med de kliniske symptomer, en fremgangsmaade, som har vist sig velegnet. For at kunne hævde, at tiouracilvirkning er indtraadt hos en patient med thyreotoxicosis, kræves saaledes saa vidt muligt et kendeligt (og fortsat) fald i stofskiftet, ledsaget af en tydelig (og fortsat) stigning i vægten under samtidig hensyntagen til bedring i det øvrige kliniske billede. Patientmaterialet gennemgaas.

Som resultat af en nøje bedømmelse af patienterne ud fra de nævnte synspunkter skal fremhæves, at der ikke synes at være nogen større forskel i virkningen af tiouracil og metyltiouracil. Tidspunktet for tiouracilvirkningens indtræden varierer stærkt. Virkningen indtræder hurtigst ved primær, ubehandlet thyreotoxicosis; kan ofte erkendes her efter 1 uges forløb, og er i reglen sikker efter omkring 2 ugers behandling; virkningen synes at indtræde hurtigst ved svære tilfælde af thyreotoxicosis. Sygdommens varig-

hed før behandlingen, patientens alder og strumas størrelse er ved de primære former uden afgørende betydning. Forudgaaende jodbehandling forsinker virkningens indtræden, undertiden ret betydeligt; tilouracilvirkningen synes endvidere at indtræde langsommere hos patienter med sekundær thyreotoxicosis og ved recidivtilfælde.

En sikker tiouracilvirkning vil i almindelighed kunne paaregnes indenfor 2—6 uger hos patienter med thyreotoxicosis.

Kapitel IV.

Hensigten med dette kapitel er at bedømme virkningen paa de thyreotoxiske symptomer under fortsat behandling med tiouracil eller metyltiouracil. Endvidere at iagttage, om behandlingen fremkalder forandringer i organismen, der ikke skyldes stoffets antithyroide virkning.

Patienterne er alle hospitalsbehandlede i kortere eller længere tid og efter udskrivelsen jævnligt kontrolleret paa hospitalet. Det foreliggende patientmateriale er som omtalt usorteret og ret begrænset og derfor isoleret ikke fuldt tilstrækkeligt til en bedømmelse af hastigheden og rækkefølgen, i hvilke de enkelte thyreotoxiske symptomer svinder under tiouracilbehandlingen. Det fremhæves, at mange ydre forhold i høj grad kan influere paa patientens i forvejen labile psyke og derigennem paa hele patientens tilstand.

Forfatteren naar til det resultat, at den *psykiske og motoriske* uro er blandt de symptomer, der aftager først; *træthed og nervøsitet* (samt diarré) kan undertiden holde sig meget længe. *Pulsfrekvensen* følger i store træk faldet i stofskiftet og bedringen i almentilstanden. *Komplicerende hjertelidelse* bedres under behandlingen, hurtigst hvis den ikke har bestaaet gennem længere tid.

En del patienter bliver under den fortsatte behandling tilsyneladende fuldstændig symptomfri. Tidspunktet herfor varierer stærkt. Det skal dog fremhæves, at behandlingsresultatet hos en del patienter ikke bliver tilfredsstillende, idet lette thyreotoxiske symptomer vedbliver at bestaa.

Det *forhøjede stofskifte* falder i reglen til normale værdier under

behandlingen, og *vægten stiger* undertiden til uønsket høje værdier. Doseringens betydning omtales ganske kort.

Struma: Vanskeligheden ved at bedømme strumas forhold omtales. En afgørende formindskelse af struma er ikke iagttaget hos nogen af de her omtalte patienter, derimod voksede struma hos 7; hos 2 af disse skete væksten i tilslutning til overdosering, der gav anledning til en hypothyroid tilstand. Væksten af struma her er analog med strumadannelsen hos rotter, der behandles med tiouracil. 3 patienter er blevet opereret paa grund af voksende struma.

Exoftalmus er i reglen aftaget under behandlingen og hos enkelte patienter svundet fuldstændigt. Exoftalmus svinder undertiden langsomt, og hos en patient bestod en let exoftalmus uforandret efter $^1/_2$ aars behandling.

Hos patienterne er der med visse mellemrum foretaget en række *laboratorieundersøgelser* for herigennem evt. at afsløre bivirkninger af behandlingen.

Der er ikke under behandlingen paavist *albuminuri* hos patienterne.

Blodurinstof og *blodsukker* har altid vist normale forhold. Nogen indvirkning paa *blodsænkningen* eller *hæmoglobinprocenten* er ikke iagttaget.

Thrombocyttallet er hos ialt 3 patienter faldet til under 100000 (minimum 70000), og hos ialt 19 patienter er antallet af *hvide blodlegemer* under behandling med tiouracil og metyltiouracil faldet til under 4000 pr. mm^3 (minimum 2040).

Differentialtælling har hos nogle faa patienter vist lymfocytær overvægt med procentvis fald i antallet af granulocyter til minimum 36 %. Der er aldrig iagttaget granulocyttal paa under 1000 pr. mm^3. Der er aldrig hos patienterne iagttaget kliniske tegn paa thrombopeni eller paa agranulocytose.

Serumkalkbestemmelser har hos 16 patienter vist fald i værdierne til under 9,5 mg%, hos 8 patienter til under 8,5 mg%, den mindste iagttagne værdi er 7,2 mg%. Der har ikke været kliniske tegn paa hypocalcæmi.

Serumcholesterolværdierne er hos enkelte patienter steget ret

stærkt, men har hos de fleste patienter holdt sig indenfor normale værdier.

De enkelte afsnit indenfor dette kapitel diskuteres. Det fremhæves, at subjectiv symptomfrihed ingenlunde altid er ledsaget af objectiv symptomfrihed, idet bl. a. struma og exoftalmus ofte persisterer.

Tiouracilbehandlingens eventuelle kurative effekt omtales; ingen af de behandlede patienter er blevet helbredt indenfor den angivne observationstid.

Præoperativ tiouracilbehandling.

Tiouracil eller metyltiouracil er anvendt som præoperativt behandlingsmiddel hos ialt 19 patienter, hvoraf en del er langvarigt behandlet. Patientmaterialet gennemgaas; særlig omtales en patient, hvor tiouracilbehandlingen havde en næsten mirakuløs virkning paa den svære thyreotoxiske tilstand, efter at patienten havde været behandlet forgæves paa hospital i 19 maaneder. Hos 2 patienter forværredes de thyreotoxiske symptomer, idet ineffektiv jodbehandling blev afbrudt samtidig med, at tiouracilbehandlingen paabegyndtes; denne fremgangsmaade bør derfor muligvis undgaas.

Hvor tiouracil eller metyltiouracil andvendes som eneste præoperative behandlingsmiddel, forefindes ved operationen en stærkt vascullariseret, blød og sprød thyreoideakirtel, der er ubehagelig at operere paa. Jodtilførsel før operationen ændrer dette forhold, hvorfor jodtilførsel præoperativt maa anbefales. 1 uges jodbehandling samtidig med tiouracilbehandlingen før operationen synes at være fuldt tilstrækkelig, og der synes ikke at være nogen forskel paa operationsresultatet ved afbrydning af tiouracilbehandlingen 1 uge før operationen, paa operationsdagen eller 1 uge efter.

Det anses ikke for nødvendigt at udskyde operationen, til de thyreotoxiske symptomer er svundet, og stofskiftet er blevet normalt. Eksempel herpaa gives. Faren for postoperativ, thyreotoxisk krise reduceres.

Jodvirkningens indflydelse paa thyreoidea hos thyreotoxicosepatienter omtales. Tiouracilvirkningen paa thyreoidea er af en anden natur end jodvirkningen og bringer ingenlunde den hyper-

plastiske glandel i et roligt stadium. Det histologiske billede, man ser efter selv langvarig tiouracilbehandling, er i mange henseender identisk med den ubehandlede, thyreotoxiske strumas udseende. De lymfatiske infiltrater synes dog mindre udtalte. Disse forhold tyder paa, at tiouracilvirkningen ingen inflydelse har paa den accelererende faktor ved thyreotoxicosis. Af denne grund anser man ikke tiouracilvirkningen i sig selv for at have direkte, kurativ effekt overfor thyreotoxicosis. Derimod kan behandlingen muligvis, ved at genskabe normale forhold i organismen med hensyn til thyreoideahormonets mængde, indirekte foraarsage, at den ukendte, accelererende faktor paa en eller anden maade ophører med at udøve sin virkning paa thyreoidea.

Kapitel V.

I dette kapitel gøres doseringsspørgsmaalet til genstand for en grundig omtale. Resultater fra de experimentel-biologiske undersøgelser, der har betydning for doseringen, omtales. 0,6 g tiouracil eller metyltiouracil daglig *(0,2 g × 3)* maa anses for velegnet som begyndelsesdosis, en større dosis synes ikke at give en tilsvarende øget effekt. Af hensyn til bivirkninger bør begyndelsesdosis reduceres saa hurtigt som muligt, selv om dette vil bevirke, at tidspunktet for opnaaelse af symptomfrihed udskydes.

Princippet i behandlingen maa være hurtigst muligt at bringe dosis ned paa mindst mulige størrelse, der er i stand til fuldt ud at kontrollere den thyreotoxiske tilstand.

Som vedligeholdelsesdosis er dels anvendt 0,2 — 0,1 — 0,05 g tiouracil eller metyltiouracil daglig eller 0,2 g hveranden, hvertredie eller hverfjerde dag. Disse doser har hos en del patienter vist sig velegnede som vedligeholdelsesdosis. Det fremhæves dog, at en for lille vedligeholdelsesdosis muligvis er skyld i, at de thyreotoxiske symptomer hos en del patienter ikke er svundet fuldstændigt, eller senere under behandlingen er begyndt at recidivere. En individualiseret behandling anses for meget vigtig.

Overdosering er iagttaget og gav hos 1 patient anledning til fremkomsten af veludtalte myxodematose symptomer; den omtalte patient fik som vedligeholdelsesdosis 0,1 g metyltiouracil daglig, hvilket viste sig utilstrækkeligt; 0,2 g daglig fremkaldte imidlertid

i løbet af 1 maaned svær overdosering med stofskiftefald til ÷ 38 %. Der er ikke fundet nogen kvalitativ forskel i virkningen af tiouracil og metyltiouracil, derimod en ringe kvantitativ forskel, som dog ingenunde svarer til forskellen i virkningen af de to stoffer i de experimentel-biologiske forsøg.

Kapitel VI.

Bivirkninger. De experimentel-biologiske undersøgelser omtales. Under behandling med tiouracil og metyltiouracil er patienterne observeret nøje med henblik paa bivirkninger. Der skelnes mellem uønskede reaktioner under behandlingen, reaktioner, som ikke med sikkerhed kan tillægges denne, og bivirkninger, der er en direkte følge af behandlingen.

Naar der hos ialt 19 patienter en eller flere gange under behandlingen er indtraadt et fald i antallet af hvide blodlegemer til under 4000 pr. mm^3, kan dette ikke uden videre betegnes som bivirkning, men forholdene giver en værdifuld oplysning.

Ved en nøje gennemgang af de 54 patienter har man hos ikke mindre end 43 iagttaget een eller flere uønskede reaktioner (incl. egentlige bivirkninger): hos 7 patienter voksede struma; 7 patienter fik temperaturstigning; 4 patienter smagsforstyrrelse; 3 patienter kvalme; 1 patient myalgier; 2 patienter arthralgier; 4 patienter hudexanthem; 3 patienter ødemer i huden. Hos 19 patienter faldt antallet af hvide blodlegemer til under 4000 pr. mm^3; hos 4 af disse patienter til under 3000 pr. mm^3 (laveste værdi 2040 pr. mm^3). Hos 28 patienter fandtes thrombocyttal under 200000, hos 3 af disse paa under 100000 (laveste værdi 70000 pr. mm^3).

Hos ialt 18 patienter (33 %) er der under behandlingen afsløret uønskede reaktioner af en saadan art og i et saadant antal, at man anser det for berettiget at tale om bivirkninger, et forhold, der berigtiges derigennem, at bivirkningerne regelmæssigt er svundet eller aftaget samtidig med, at man enten har reduceret dosis eller afbrudt behandlingen. Bivirkningerne er fortrinsvis optraadt indenfor den første maaned af behandlingen.

Der gives en oversigt over de af andre forfattere iagttagne bivirkninger samt hypigheden af disse hos patienterne. Det viser sig, at der under behandlingen kan optræde ialt ca. 20 forskellige bi-

virkninger af mere eller mindre alvorlig karakter. Forandringerne i blodbilledet synes ikke blot at høre til de hyppigste bivirkninger, men maa uden tvivl betragtes som de alvorligste. Virkningen paa knoglemarven har i adskillige tilfælde haft dødelig udgang til følge.

Behandlingen af thyreotoxicosis med tiouracil og metyltiouracil er en betydningsfuld landvinding for lægevidenskaben. De nævnte stoffer har ingen større toxisk virkning paa forsøgsdyr. I kraft af deres antithyroide effekt kan de med ret stor regelmæssighed bringe de thyreotoxiske symptomer til at aftage eller svinde fuldstændigt, og kan muligvis indirekte fremkalde helbredelse af sygdommen.

Stofferne har endvidere stor værdi overfor thyreotoxicosepatienter, hvor jodbehandling ikke har vist effekt, ligesom de i forbindelse med jodbehandling er velegnede som præoperativt behandlingsmiddel, idet faren for den thyreotoxiske krise reduceres.

De hyppigt optrædende bivirkninger under behandling med disse stoffer nødvendiggør imidlertid, at patienterne nøje overvaages, særligt med henblik paa forandringer i blodbilledet. Da bivirkningerne særligt optræder indenfor den første maaned, hvor den største dosis anvendes, maa det anses for onskeligt, at behandlingen indledes paa et hospital. Bestræbelserne i fremtiden maa gaa ud paa at finde frem til stoffer, der har samme effekt, men er uden toxisk virkning paa den menneskelige organismne.

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